

# THE American Journal OF Gastroenterology

VOL. 21, NO. 1

JULY, 1955

The Early Operative Treatment for Gastric Hemorrhage  
Cholinergic Blocking Agents on the Gastrointestinal Tract  
The Nonsurgical Mortality of Carcinoma of the Stomach  
Carcinoma of the Cecum

Hyperchlorhydria—Can it be Controlled Medically

Newer Clinical and Laboratory Studies in the Aged,  
VII—Tubeless Gastric Acidity Determinations  
in Normal Geriatric Subjects

Massive Hemorrhage Due to Diverticula of the Colon

**Second Annual Convention**

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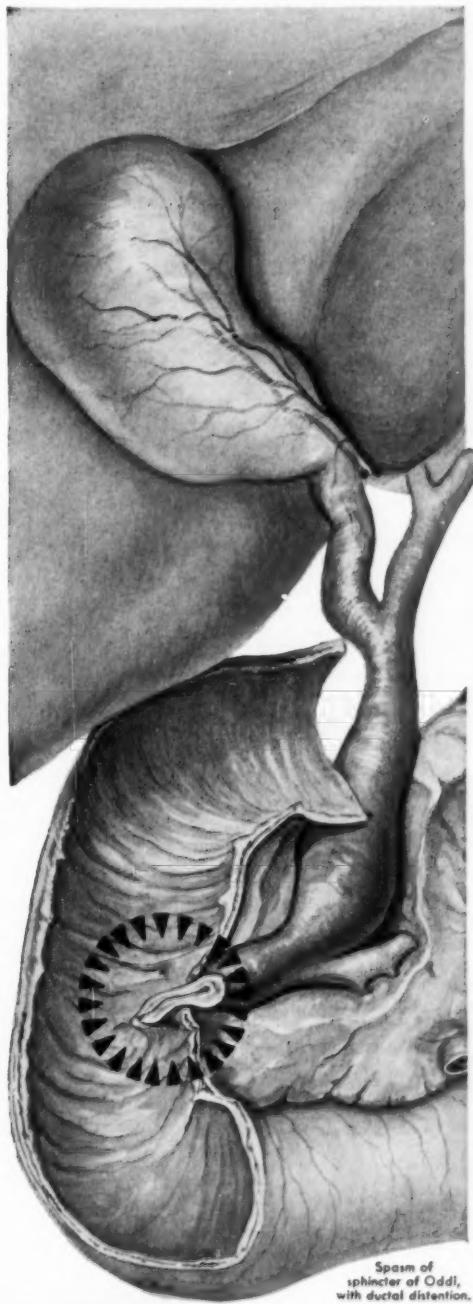
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(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

*The Pioneer Journal of Gastroenterology, Proctology  
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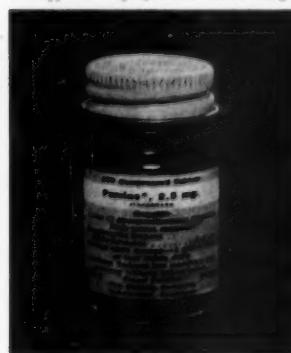
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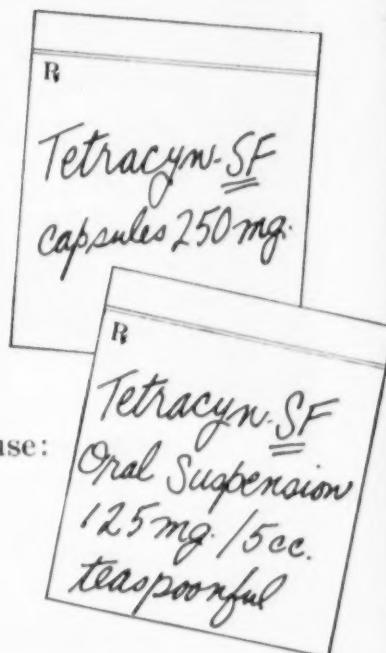
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2. Martí-Ibáñez, F.: Antibiotic Med. 1:247 (May) 1955.
3. Dumas, K. J.; Carlozzi, M., and Wright, W. A.: Antibiotic Med. 1:296 (May) 1955.

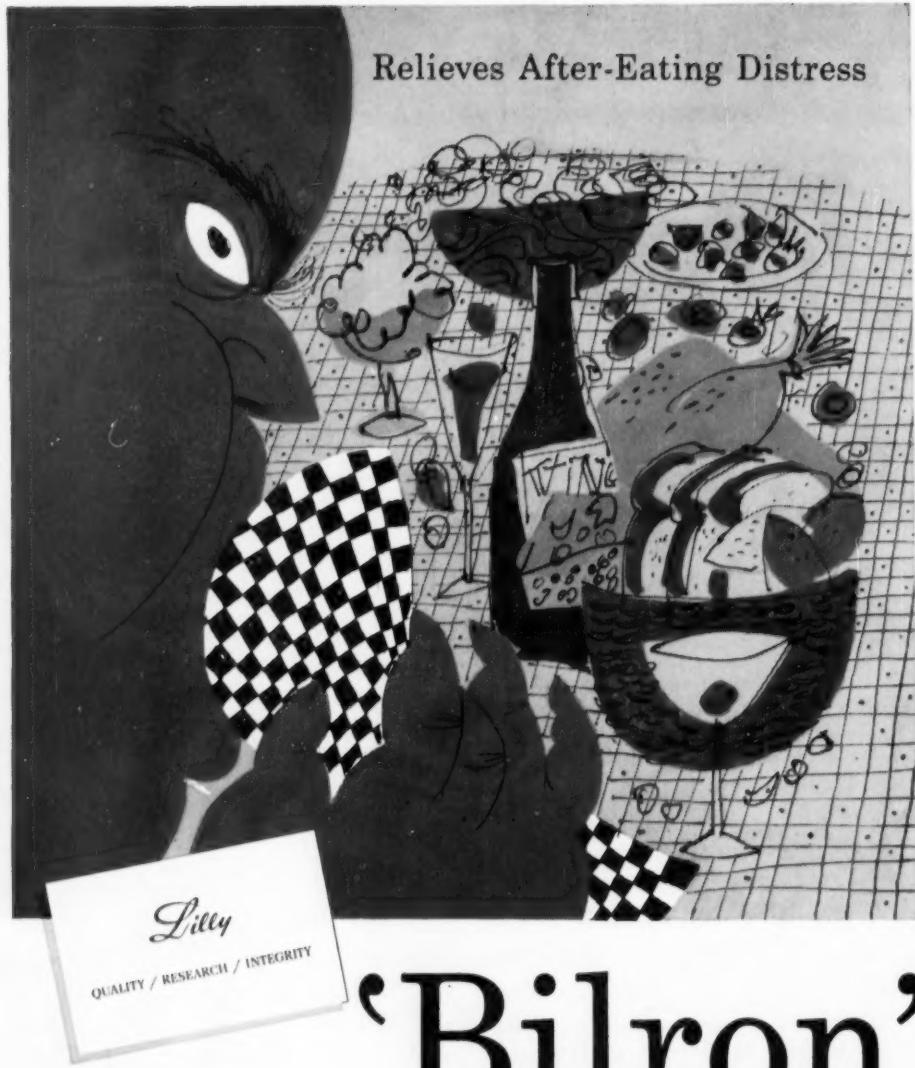


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Nausea and vomiting, hiccups, pylorospasm	104									80%	
Hiatal hernia, gastro-duodenitis, upper gastrointestinal bleeding	15									87%	
Gastritis medicamentosa	8									100%	
Genito-urinary disorders	23									74%	
Postoperative nausea and vomiting	15									90%	
Nausea and vomiting of pregnancy	7									71%	
Gall bladder disorders	10									80%	

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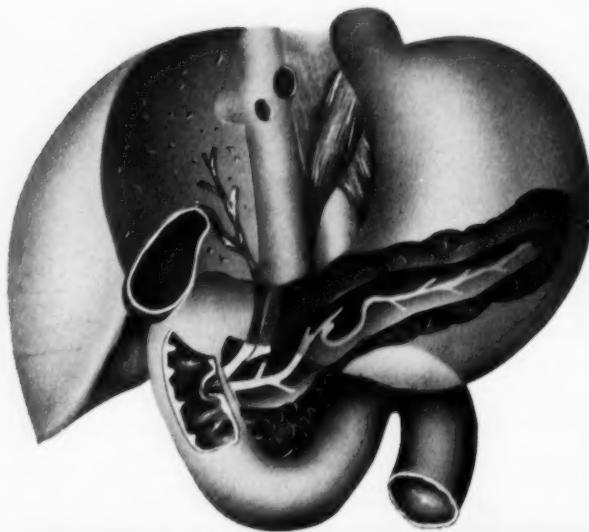
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## THE EARLY OPERATIVE TREATMENT FOR GASTRIC HEMORRHAGE\*

JULES D. GORDON, M.D., F.A.C.S., F.A.C.G.  
New York, N. Y.

Burrill Crohn<sup>1</sup>, at a meeting of the Section on Gastroenterology and Proctology in 1952, said and I quote, "that it is becoming increasingly clear that a completely passive attitude toward upper gastrointestinal bleeding is no longer tenable. The older approach of expectant optimism, bed rest and starvation seems inadequate in the face of massive and continuing hemorrhage."

Not all gastroenterologists, however, share this opinion. The conservative-minded internist who rejects emergency surgery for the severely bleeding case does so, having in mind his own overall small mortality rate. In his review of the literature he may find support of his views in other statistical reports which reveal equally small overall mortality rates. The disturbing elements to such a point of view are that the actual number of deaths is not insignificant, that many of these deaths are avoidable, and that the importance of these deaths has inadvertently been minimized by their inclusion in a large series of cases, most of which are cases of insignificant bleeding. Since it is only the severe bleeding ulcer case that may become a fatality, it must be the concern of the internist and the surgeon to direct his attention to this type of case. He must not permit himself to be lulled into a false sense of security by quoted series of low mortality rates which include all bleeding ulcer cases. These series serve only to becloud the issue of the high mortality rate of the severe bleeders.

### STATISTICAL VARIATIONS ACCORDING TO TYPES OF BLEEDERS

The 25-year old controversy of medical versus surgical treatment has largely been the result of such improper focusing. The image of distortion is understandably increased by the 1.5 per cent mortality rate reported by Meulengracht<sup>2</sup> and the 74 per cent mortality rate reported by Chiesman<sup>3</sup>. Meulengracht reported ulcer cases with all degrees of bleeding while Chiesman's mortality

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\*Read before the First Annual Convention of the American College of Gastroenterology, Washington, D. C., 25, 26, 27 October 1954.

rate of 74 per cent is based only on those ulcers with an exsanguinating type of hemorrhage. Thus it becomes apparent that the variation in reported mortality statistics is dependent upon the types of cases included in such reporting. This emphasizes the need, when quoting mortality statistics, to compare only similarly constituted series. An example of how varying mortality statistics are dependent upon types of cases included can be demonstrated by a breakdown of our 71 bleeding ulcer cases according to classification of types of bleeders and their respective mortality rates (Table I).

There were 71 bleeding ulcer cases admitted to our hospital during a five-year period. This included bleeding of all degrees. There were five deaths among

TABLE I  
MORTALITY RATES IN BLEEDING ULCERS  
(STATISTICAL VARIATION IN SINGLE SERIES)  
BETH DAVID HOSPITAL 5 YEARS—1949-1954

Type of Bleeding	Type of Treatment	# of Cases	# of Deaths	% Mortality
All degrees of bleeding	Conservative and surgical	71	5	7.1
All degrees of bleeding	Conservative	60	5	8.3
Moderate and Massive Bleeders (cases requiring at least 1 transfusion)	Conservative and surgical	59	5	8.4
Moderate and Massive Bleeders	Conservative	48	5	10.4
Massive Bleeders (cases with hemoglobin below 50% and red blood cell count below 2.5 million)	Conservative and surgical	23	5	21.9
Massive Bleeders	Conservative	12	5	41.6

these cases with a resultant mortality rate of 7.1 per cent. If we considered moderate and severe bleeders only—that is cases requiring at least one transfusion for correction of the anemia caused by their bleeding—12 cases of very mild bleeding would be excluded. This would give us a mortality rate of 8.4 per cent for the five deaths in the 59 cases of moderate and massive bleeders. If, however, we presented our massive hemorrhage cases only, there would be 23 cases with five deaths or a mortality rate of 21.9 per cent. Our mortality rates, under conservative treatment which excludes 11 cases operated upon without a mortality, gives us the following figures for each category of bleeder: for all bleeders—five deaths in 60 cases—a mortality rate of 8.3 per cent; for the moderate and massive bleeders—five deaths in 48 cases or a mortality rate

of 10.4 per cent for massive bleeders—five deaths in 12 cases or a mortality rate of 41.6 per cent. To test the validity of these figures as an example of what can be done to a series of bleeding ulcer cases of selected types, I have chosen to break down Bohrer's<sup>4</sup> report on bleeding ulcers. I have selected this series because his hospital is similar to ours in size, economic status of its hospital population, and possessed of a like ambulance service. His report in 1941 dealt with 182 bleeding ulcer cases admitted during a 10 year period (Table II). There were 14 deaths in this group giving a mortality rate of 7.6 per cent—our mortality rate, you will recall, was 7.1 per cent. Eighty cases were described as massive hemorrhage cases and defined by the same criteria that I have adopted for our massive hemorrhage cases. All of the 14 deaths occurred in this group,

TABLE II  
MORTALITY RATES IN BLEEDING ULCERS  
(COMPARATIVE STUDY)

Type of Bleeding	Author	# of Cases	# of Deaths	% Mortality
All degrees of Bleeding	Present Series July 1, 1949-July 1, 1954 (5 years)	71	5	7.1
	Bohrer's Series <sup>4</sup> 1931-1940 (Incl.) (10 years)	182	14	7.6
Massive Hemorrhage  (Hb. below 50% R.B.C. below 2,500,000)	Present Series	23	5	21.9
	Bohrer's Series <sup>4</sup>	80	14	17.5

giving a mortality rate of 17.5 per cent—our mortality rate for this category was 21.9 per cent. All but four of his cases were treated conservatively. There was one death among the four cases operated upon. It is interesting to note that there were no fatalities among the nonmassive hemorrhage cases in either Bohrer's or our series. This again emphasizes that it is the cases of massive gastric hemorrhage which are our major concern and that it is the mortality statistics for this group of cases that must be looked at if one is to get a proper perspective of the gravity of the problem and the need for an aggressive approach to reduce this high mortality.

#### MORTALITY OF MASSIVE HEMORRHAGE BY CONSERVATIVE TREATMENT

This important problem of massive gastric hemorrhage can best be appreciated when one reviews some of the reported mortality statistics of massive hemorrhage treated by conservative methods (Table III). Chiesman<sup>5</sup>, in 1932, reported on 191 cases of massive hemorrhage with 46 deaths—a mortality rate

of 27 per cent. He quotes Hinton with a 20 per cent mortality rate for 52 cases, Ross of Melbourne—58 per cent mortality in 45 cases and Lynch of Canada 12.9 per cent mortality in 31 cases. In 1941 Bohrer<sup>4</sup>, as previously quoted, reported on 80 cases of massive hemorrhage, 76 of these were treated conservatively with 13 deaths or a mortality rate of 17.1 per cent. Amendola<sup>5</sup>, in 1949, reported on 84 cases collected at the Roosevelt Hospital with 13 deaths or a mortality rate of 15 per cent. Stewart<sup>6</sup>, in 1950, reported a 21.4 per cent mortality rate in 42 cases of massive hemorrhage treated by conservative methods.

From the aforementioned statistics it is evident that there is a real need for a more aggressive approach in the treatment of massive bleeding cases in order to reduce their high mortality rate. Before proceeding with a discussion of this problem a definition of the term "massive gastric hemorrhage" is essential.

TABLE III  
MORTALITY RATES OF MASSIVE HEMORRHAGE CASES  
UNDER CONSERVATIVE TREATMENT

Author	Number of Cases	% Mortality
Chiesman <sup>3</sup> 1932	191	27
Hinton	52	20
Ross	45	58
Lynch	31	12.9
Bohrer <sup>4</sup> 1941	80	17.1
Amendola <sup>5</sup> 1949	84	15.0
Stewart <sup>6</sup> 1950	42	21.4
Present Report 1954	12	41.6

According to Stewart's definition "massive" bleeding means an acute bleeding of such severity as to lower the total circulating red cell mass to less than 60 per cent of normal. This definition is broad enough to encompass all types of severe bleeders. Every case of massive bleeding, as just defined, however, is not a candidate for surgery for it is apparent from the figures just quoted that approximately only 20 per cent of the cases will die under conservative treatment. It should be our aim, therefore, to establish a set of criteria that can be used for the detection of the massive hemorrhage case that may become a fatality. Stewart<sup>6</sup>, on the other hand, operates on every ulcer case with massive hemorrhage within the first 48 hours if consent is obtained. His point of view is not without some justification if one looks at his results. He reported that of the 65 cases of massive hemorrhage operated upon during the bleeding phase there were seven deaths—a mortality rate of 10.7 per cent. During this same period there were 42 cases of massive hemorrhage who refused surgery of which nine died—a mortality rate of 21.4 per cent. In spite of these convincing statistics it

is still the policy of most surgeons to operate only upon those massive hemorrhage cases which could conceivably exsanguinate.

#### OPERATIVE MORTALITY DURING BLEEDING PHASE

The recent reports of the results of early operation performed on cases of massive hemorrhage to prevent exsanguinating hemorrhage, are heartening (Table IV). Finsterer<sup>7</sup>, in 1939, reported a 5.6 per cent mortality rate for 78 cases which were operated upon during the first 48 hours of active bleeding. Gordon Taylor<sup>8</sup>, in 1934, reported on 22 cases operated upon during their active bleeding with 2 fatalities or a mortality rate of 9 per cent and in 1946<sup>9</sup> he reported on 18 cases with one death or a 5.5 per cent mortality rate. Amendola<sup>10</sup>, in 1949, operated upon 11 cases of uncontrollable bleeding within 48 hours

TABLE IV  
MORTALITY OF EARLY GASTRIC SURGERY  
DURING BLEEDING PHASE

Author	Number of Cases	% Mortality
Finsterer <sup>7</sup> 1939	78	5.6
Gordon Taylor 1934	22	9.0
1946 <sup>9</sup>	18	5.5
Amendola <sup>10</sup> 1949	11	9.0
1952	38	2.6
Stewart <sup>6</sup> 1950	65	10.7
Last 50 cases	50	6.0
Gordon 1954	11	0.0

with a mortality rate of 9 per cent. Stewart<sup>6</sup>, in 1950, reported on an operative mortality rate of 6 per cent in 50 consecutive cases of acute massive hemorrhage and a 10.7 per cent mortality in his last 65 cases operated upon. Amendola<sup>10</sup>, in 1952, reported a mortality rate of 2.6 per cent in 38 cases of massive bleeding from ulcer operated upon during the bleeding phase. Crohn<sup>1</sup> collected 805 cases of massive ulcer hemorrhage upon which emergency surgery was performed within the first 48 hours. The overall average mortality rate was 10 per cent. During the last five years in our series we operated upon 11 cases of massive hemorrhage during the active bleeding stage with no mortality.

These figures are in sharp contrast with the mortality figures for surgery performed in the late stages when conservative therapy had failed or where the patient was practically exsanguinated. The following figures are examples of this high mortality rate: Lynch of Montreal, 42.8 per cent; Finsterer, 26.9 per cent<sup>7</sup>; Heuer, 70 per cent<sup>10</sup>; and Gordon Taylor, 59 per cent<sup>8</sup>. It could be argued

that even these high mortality rates are preferable to the potential 75 per cent mortality for the massive hemorrhage case who is exsanguinating under conservative treatment. The mortality rate of 75 per cent reported by Chiesman<sup>3</sup> was based on just such cases.

#### INDICATIONS FOR SURGERY IN MASSIVE HEMORRHAGE

From the experience gained in a study of the bleeders in our series as well as from a study of the fatalities in other series, a set of indications for early gastric surgery can be formulated. To be sure there will be some errors of omission and commission in any set of formulated dicta but I feel that the indications to be listed will be broad enough to detect every potential exsanguinator.

*The indications for early surgery in the massive hemorrhage case are:—*

1. A patient with visible gross massive hemorrhage from the gastrointestinal tract whose blood picture of massive hemorrhage or signs of shock are not rapidly corrected by adequate transfusion soon after admission is a candidate for very early gastric surgery.
2. A patient, under indication 1, who, after apparent stabilization, has a recurrence of bleeding as evidenced by the blood picture, signs of shock and/or gross external bleeding from the gastrointestinal tract is a candidate for immediate gastric surgery.
3. A patient who enters the hospital without signs of active bleeding but with a history of having had recent massive gross bleeding is a candidate for immediate gastric surgery if signs of fresh bleeding occur as evidenced by massive external bleeding, signs of shock or a lowering of the blood count and hemoglobin.
4. A patient who enters the hospital with signs of massive hemorrhage who is stabilized as judged by his clinical condition and blood picture but who requires more than 1,500 c.c. of blood per diem for 2 or more days to maintain this stabilization is a candidate for early gastric surgery.

#### ANALYSIS OF CASES

Analysis of our cases will help to demonstrate the workability of these indications. Only cases of gastrointestinal bleeding due to peptic ulcer were included in our series, care being taken to exclude bleeding as a result of esophageal varices, tumors of the stomach and blood dyscrasias.

During the five-year period between July 1, 1949 and July 1, 1954 there were 623 cases admitted to our hospital with a diagnosis of peptic ulcer. Fifty-nine of these cases were admitted as bleeding ulcers and required at least one transfusion for the correction of the bleeding. Twenty-three of these 59 cases were

cases of massive hemorrhage and 11 of these 23 cases came to early surgery for the correction of the bleeding. Five of the 12 cases of massive hemorrhage treated conservatively died. The analysis of these 5 cases follows:

**ANALYSIS OF FATAL CASES OF MASSIVE HEMORRHAGE  
UNDER CONSERVATIVE TREATMENT (Table V)**

*Case 1:-(#49-2791)-C. L., a male, aged 34, was admitted to the hospital on June 6, 1949 in severe shock vomiting copious amounts of fresh red blood.*

TABLE V  
ANALYSIS OF FATALITIES IN MASSIVE HEMORRHAGE CASES

Case	Sex	Age	Chief Complaint	Prev. History	Shock	B.P. & Pulse	Bld. Cnt.	Cat.	Time: Admission to Death	Avoidable or Unavoidable
Case 1 C.L.	M	34	Hematemesis 24 hrs.	Prev. bleeding episodes Pain—1 yr.	4+	0	0	1	2 hrs.	U
Case 2 M.K.	M	63	Mild shock	Known Peptic ulcer 1 yr. Severe vomiting of blood 2 days before admission.	2+	120/92	Hb. 97% 4.9M	2	3 days	A
Case 3 G.B.	M	40	Melena, Hematemesis Dizziness Fainting 10 days	12 yrs. Peptic ulcer Perforation 12 years ago.	3+	80/60 120	67% 4.4M	1	17 hrs.	A?
Case 4 M.J.	F	42	Melena, Bloody vomiting Weakness 14 hrs.	Gastric hemorrhage 2 yrs. ago Epigastric pain 5 wks.	2+	70/50 130	32% 2.1M	2	2½ days	A
Case 5 A.D.	M	65	Confusion Restlessness 24 hrs.	Melena 8 mos.	3+	70/0 ?	34% 2.3M	1	16 hrs.	U?

The pulse and blood pressure were unobtainable. The patient had been vomiting copious amounts of blood for 24 hours. There was a previous history of epigastric pain and bleeding episodes of one year's duration. The patient expired 2 hours after admission to the hospital.

*Comment:*—No therapy would have been of avail during the short hospital stay. This case would have fallen into our first category and death may have been avoided had the patient been admitted at least 12 hours sooner and had urgent surgery been performed.

*Case 2:*—M. K., a male, aged 63, was admitted to the hospital on May 26, 1949 in mild shock (i.e. pallor and weakness). The blood pressure was 120/92, the hemoglobin was 97 per cent with 4.9 million red blood cells. The patient gave a history of an episode of copious hematemesis 2 days before admission. There was a past history of pain from a known peptic ulcer for one year. On May 29, 1949 at 5 P.M., three days after admission, the patient began to vomit fresh red blood, the loss was estimated at 1,000 c.c. The patient was pale, cold and covered with perspiration. The pulse rate was 140 and the blood pressure 80/40. Recovery from shock was prompt after an immediate plasma transfusion. The patient had another bout of vomiting fresh red blood 4 hours later. The blood pressure at that time was 140/80 and the pulse 108. A transfusion of 500 c.c. of blood was given. On May 30, 1949, four days after admission, the patient's condition was described as "satisfactory". At that time the red blood cell count was 4.1 million and the hemoglobin 84 per cent. The next day the patient had another bout of vomiting fresh red blood and clinical signs of shock were evident—the pulse rate was 140 and the blood pressure 80/60. The general condition was described as poor. The blood count revealed a hemoglobin of 82 per cent and a red blood cell count of 4.0 million. A transfusion of 500 c.c. of blood was given after which the patient's condition was described as "satisfactory with bleeding under control". At 9:30 P.M. that night the patient had another episode of vomiting of blood and again showed signs of shock. The pulse rate was 140 and the blood pressure was 80/60. Two units of plasma and 1,000 c.c. of blood were administered. The next day, June 1, 1954, in the morning, the blood pressure was 160/80. That afternoon at 3:00 P.M. the patient vomited about 300 c.c. of fresh red blood mixed with clots. One thousand c.c. of blood and 1 unit of plasma were given. Despite continued transfusion the patient did not recover from shock and died two days later immediately after another episode of bloody vomitus.

*Comment:*—An indication for early surgery existed with the first recurrence of hematemesis after a severe episode of hematemesis two days before admission. Delay was possibly justified because of what seemed to be a relatively normal blood picture and the absence of signs of marked shock on admission. A second episode of recurrent bleeding 4 hours later, accompanied by signs of shock, should have made surgery mandatory. It is interesting to note that hemoconcentration was persistent during his entire period of bleeding and shock. This is not an unusual occurrence in severe bleeding cases and should never deceive the clinician. Severe acute anemia must be suspected when a relatively normal blood count is present in a patient who has lost a great deal of blood and shows signs of shock. This death may have been avoidable if

early surgery had been performed in observance of rule 3 of indications for surgery as previously set forth in this paper.

*Case 3:*—G. B., a male, aged 40, was admitted to the hospital on April 2, 1950 at 10:30 A.M. with a ten day history of melena, hematemesis, dizziness and fainting. On admission, the patient was pale, the blood pressure was 80/60, the pulse rate 120, the hemoglobin 67 per cent and the red blood cell count 4.4 million. The patient suffered with a known peptic ulcer and had an episode of perforation 12 years previously. He was given 3 units of plasma during the first 8 hours after admission during which time he continued to have tarry stools. At 6:00 P.M. the patient appeared to be in a condition of moderate shock. A transfusion of 1,000 c.c. of blood was started. At 11:30 P.M. the blood pressure was 106/70 and the pulse rate 120. A note was made at this time that the blood pressure was being maintained only by continuous blood transfusion. Two thousand c.c. of blood was added but the patient expired at 3:15 A.M. on April 3, 1950, 17 hours after admission.

*Comment:*—The blood picture on admission, in view of the clinical picture, was not misleading, hemoconcentration existed and the patient should obviously have had whole blood instead of plasma during the first eight hours. The signal for early surgery was present at 6:00 P.M. when he went into shock but this point is debatable since adequate blood replacement was not employed. At 11:30 P.M. after 1,000 c.c. of blood had been given, signs of concealed hemorrhage still existed despite the relatively elevated blood pressure. In a patient who has had a long period of bleeding prior to admission, evidence of continued bleeding without stabilization becomes a most urgent indication for early surgery. This case falls into category 1. This death may have been avoidable by surgery even 5 hours before death. Autopsy revealed an open vessel in a penetrating callous ulcer of the duodenum.

*Case 4:*—Female, M. J., aged 42, was admitted to the hospital on December 1, 1951 at 6:30 A.M. with tarry stools, bloody vomitus and weakness of 14 hours' duration. On admission the hemoglobin was 32 per cent and the red blood cell count 2.1 million. The blood pressure was 70/50 and the pulse rate 130. The past history revealed that the patient had a gastric hemorrhage requiring 4 transfusions 2 years previously and that persistent epigastric pain was present for the past 5 weeks. After 500 c.c. of plasma and 500 c.c. of blood were given the blood pressure rose to 100/60 but the pulse remained rapid at a rate of 120 per minute. At 3:00 P.M., 8½ hours after admission, the patient fainted and the blood pressure fell to 80/40, the pulse rate was 120. Five hundred c.c. of blood was given and by 7:00 P.M. the blood pressure rose to 100/60. On December 2, 1951, one day after admission, the blood pressure was recorded at 120/80, the blood count showed a hemoglobin of 44 per cent and a red blood cell count of 2.8 million. Five hundred c.c. of blood was given and the patient's general condition was described as "satisfactory". At 2 P.M. that day the patient had a bright red

bloody stool and 500 c.c. of blood was administered. At 6 P.M. the blood pressure was 120/70 and the patient's condition was reported as "satisfactory". On the morning of December 3, 1951 the hemoglobin was 62 per cent, the red blood cell count 3.7 million and the blood pressure 145/90. One thousand c.c. of blood was given. That night at 6:00 P.M. the patient vomited 350 c.c. of blood and the blood pressure was recorded at 118/58. At 11:30 P.M. the patient's blood pressure was 118/60, the pulse rate 120 and at 11:35 P.M. on December 3rd, about 60 hours after admission, the patient died. Autopsy revealed a penetrating callous ulcer of the duodenum.

*Comment:*—This case apparently responded to the initial treatment with blood and plasma but the fainting spell 8½ hours after admission was evidence that fresh bleeding had taken place. Indication existed here for immediate surgery in accordance with our second tenet. Indication for immediate surgery was again present at the time of the second recurrence of bleeding on the second day after admission. The importance of observing this dictum in this case is obvious from the end-result, for despite what appeared to be a not unsatisfactory progress in the clinical course for the next 36 hours with apparent sufficient blood replacement, the patient died.

*Case 5:*—A. D., a male of 65 years of age, was admitted to the hospital on April 9, 1951 in a restless, confused state, with extreme pallor and coolness of skin. He was described as being in shock for the previous 24 hours. He had passed tarry stools over a period of 8 months which were more severe during the week before admission. On admission his blood pressure was 70/0, his hemoglobin was 34 per cent and his red blood cell count 2.3 million. The patient was given 1,000 c.c. of blood but expired 16 hours after admission. Autopsy showed a callous gastric ulcer with an open sclerotic vessel.

*Comment:*—This death, for all practical purposes was unavoidable. Under our first indication for surgery, this patient, admitted 12 hours earlier with failure to respond promptly to adequate transfusion would have been a candidate for immediate surgery.

#### ANALYSIS OF CASES OF MASSIVE HEMORRHAGE SURGICALLY TREATED

The fate and clinical course of our 11 operative cases for massive hemorrhage in which the dicta for early surgery were observed will be outlined in brief. These cases will be presented in accordance with their surgical indications (Table VI).

*Surgical Indication 1:*—There were two cases in this category who were not promptly stabilized with adequate blood transfusions.

*Case 1:*—A female, aged 42, was operated upon within 24 hours after 3,500 c.c. of blood had failed to produce stabilizations.

TABLE VI  
ANALYSIS OF OPERATIVE CASES FOR MASSIVE GASTRIC HEMORRHAGE

Patient	Age	Sex	Indication	Time elapsed between admission to hospital & operation	Result
Case 1	42	F.	Patient received 3,500 c.c. of blood with stabilization	1 24 hours	Recovery
Case 2	38	M.	Patient received 3,000 c.c. of blood with stabilization	1 24 hours	Recovery
Case 3	52	M.	Sudden onset of bleeding after being stabilized for 5 days	2 5 days	Recovery
Case 4	54	M.	Sudden onset of fresh bleeding after 10 days of stabilization with 13 transfusions	2 10 days	Recovery
Case 5	52	M.	Severe hemorrhage before admission Stabilization for 3 days—then shock	3 3 days	Recovery
Case 6	47	M.	Patient in good condition but required 1,500 c.c. daily to maintain condition—for 5 days	4 5 days	Recovery
Case 7	22	F.	Patient required 2,000 c.c. of blood daily for 4 days to maintain stabilization	4 4 days	Recovery
Case 8	57	M.	Patient required 3,000 c.c. of blood over a 2 day period to maintain stabilization	4 2 days	Recovery
Case 9	38	M.	Patient required 2,500 c.c. of blood over a 2 day period to maintain stabilization	4 2 days	Recovery
Case 10	42	F.	Previous history of ulcer. Ten day history of bleeding 500 c.c. of blood daily to maintain equilibrium	5 7 days	Recovery
Case 11	42	M.	500 c.c. of blood daily for 5 days for stabilization	5 5 days	Recovery

*Case 2:*—A male, 38 years of age, was operated upon within 24 hours after 3,000 c.c. of blood did not produce stabilization and the patient continued to remain in a state of shock.

*Surgical Indication 2:*—There were two cases in this category, who after stabilization, had a recurrence of bleeding.

*Case 3:*—A male, aged 52, whose blood picture was stabilized for 5 days after admission. On the 6th day there was a sudden recurrence of bleeding and operation was performed within 4 hours after adequate transfusion.

*Case 4:*—A male, 54 years old. The patient was stabilized over a 10 day period by 13 transfusions of 500 c.c. each of blood. Ten days after admission sudden fresh bleeding with signs of shock occurred and prompt surgery was performed.

*Surgical Indication 3:*—There was one case which could be classified under this indication, i.e. a case entering the hospital with a history of an acute bleeding episode who, on admission, is apparently stabilized but who has a fresh bout of severe bleeding during the hospital stay.

*Case 5:*—A male, 52 years of age, who was completely stabilized for 3 days after admission for a very severe hemorrhage occurring before he was admitted. On the third day after admission, the patient went into shock after vomiting a large amount of fresh red blood. Surgery was performed promptly.

*Surgical Indication 4:*—There were four cases under this indication, i.e. those cases who required 1,000 c.c. to 1,500 c.c. of blood daily to maintain stabilization.

*Case 6:*—A male, aged 47. The patient seemed in good condition for five days but required 1,500 c.c. of blood daily to maintain him in this state. The patient was operated upon in good condition 5 days after admission.

*Case 7:*—A female, aged 22. The patient was maintained in good condition for 4 days but required 19 transfusions or about 2,000 c.c. of blood per day to maintain her status. She was operated upon on her fourth day after admission in good condition.

*Case 8:*—A male, 57 years old. This patient was stabilized but required 3,000 c.c. of blood to maintain stabilization over a 2 day period.

*Case 9:*—A male, 38 years of age. The patient was stabilized but required 2,500 c.c. of blood over a period of 2 days. The patient was operated upon on the third day after admission.

There were two cases who were just outside the limits of our 4th Surgical Indication. For purposes of clarification I shall place them under the heading of Indication 4A which can be defined as those cases which would fall under

Indication 4 except that they require less than 1,000 c.c. of blood daily to maintain equilibrium. Though only 500 c.c. of blood was needed daily, our determining factor for surgical intervention was that the blood had to be administered well beyond a 48-hour period to maintain stabilization and that there was a past history which would indicate the need for surgery at an early elective date.

*Case 10:*—A female, aged 42, who entered the hospital with a 10 day history of tarry stools. On admission the hemoglobin was 42 per cent and the red blood cell count was 2.2 million. Stabilization was achieved with 500 c.c. of blood daily for 7 days. Operation was performed on the 7th day after admission because of a long-standing ulcer history and a previous episode of bleeding 2 years before.

*Case 11:*—A male, aged 43. This patient was stabilized in 5 days with 5 transfusions. History of a previous episode of bleeding plus the present severe hemorrhage before admission became indications for surgery on the 6th day after admission.

Doubtless some of these cases which were operated upon might have recovered without benefit of surgery. The signs of continuing or recurrent hemorrhage were present in all but two cases and, by experience, one could have expected a mortality of well over 20 per cent. There was no mortality in these 11 cases.

#### ANALYSIS OF CASES OF MASSIVE HEMORRHAGE CONSERVATIVELY TREATED WITH RECOVERY

In contrast to the clinical course of those cases of massive hemorrhage under conservative treatment which became fatalities, and those cases of massive hemorrhage that came to early surgery, is the clinical course of those seven cases of massive hemorrhage that recovered under conservative treatment. The notable feature in these seven cases, with one exception, was the steady and unequivocal response to transfusions. Bleeding was promptly controlled with transfusions of 1,000 c.c. to 1,500 c.c. of blood daily. Signs of concealed hemorrhage with the accompanying evidence of shock were absent. Episodes of recurrent bleeding were absent and, at no time, did one get the general clinical impression that these patients would exsanguinate or that they would not handle their blood losses well by modest blood replacements. The hemoglobin and red blood cell count, on the other hand, were similar to those found on admission in our mortality and operative groups. It is significant that there were no cases which showed hemoconcentration. There was no important difference in the ages and sexes of the patients among these three groups. An average of five transfusions per patient was required, in this conservatively treated group of cases of massive hemorrhage who recovered, to bring their blood levels to normal.

This group of conservatively treated cases of massive hemorrhage with recovery is, in turn, in sharp contrast with those cases of bleeding with blood

pictures just above the arbitrary blood levels for our massive hemorrhage cases. It is interesting that this group of moderate bleeders required never more than a total of three transfusions over a period of two to three days. The responses were always satisfactory and prompt. There were 46 cases of moderate bleeders for whom surgical intervention was never even a consideration.

**THE ROLE OF AGE AS RELATED TO THE SEVERITY  
OF BLEEDING IN PEPTIC ULCER (Table VII)**

I have analysed our cases in categories to see whether any relationship exists between the severity of bleeding and the age of the patients.

*Fatal Cases:*—In our fatal cases the youngest patient was 34 years old and the oldest patient was 63 years old. Three of the five patients were under 45 years of age and two were over 45 years of age. The mean age was 47.

TABLE VII  
ANALYSIS OF BLEEDING CASES WITH REFERENCE TO AGE

Type of Bleeder	Treatment Employed	# of Cases	Under 45	Over 45	Youngest Age	Oldest Age	Mean Age
Fatal Massive Hemorrhage Cases	Conservative Treatment	5	3	2	34 yrs.	63 yrs.	47 yrs.
Massive Hemorrhage Cases	Surgical Treatment (Gastrectomy)	11	6	5	22 yrs.	57 yrs.	45 yrs.
Massive Hemorrhage Cases (with recovery)	Conservative Treatment	7	5	2	26 yrs.	68 yrs.	42.2 yrs.
Moderate Bleeders (requiring at least one transfusion)	Conservative Treatment	36	12	24	27 yrs.	67 yrs.	49.2 yrs.

*Cases Undergoing Urgent Surgery:*—An analysis of the ages of our 11 operative cases revealed that six cases were under the age of 45 and five cases were over the age of 45. The youngest was 22 and the oldest was 57. The mean age was 48.

*Cases of Massive Hemorrhage Conservatively Treated with Recovery:*—Of the seven cases of massive hemorrhage conservatively treated who recovered, there were five cases under the age of 45 and two cases over 45 years of age. The youngest was 26 and the oldest was 68. The mean age for this group was 42.2.

*Cases of Moderate Bleeding:*—Among those 36 cases who were moderate bleeders the youngest was 27 years of age and the oldest was 67 years of age. There were 12 cases under the age of 45 and 24 cases over the age of 45. The mean age was 49.2 years.

*Comment:*—The popular conception that bleeding is more prevalent and dangerous among those above the age of 45 is not borne out by the foregoing figures. It is permissible from this study to say that the tempering of treatment according to the age of the patient would be unsafe.

#### ROLE OF SEX AS RELATED TO THE SEVERITY OF BLEEDING

Similarly a study of sex as a determining factor in the choice of treatment was made (Table VIII).

TABLE VIII  
ANALYSIS OF BLEEDING CASES WITH REFERENCE TO SEX

Type of Bleeder	Treatment Employed	# of Cases	Males	Females	Proportion
Moderate Massive	Conservative and Surgical	59	45	14	3:1
Massive Hemorrhage Cases	Conservative and Surgical	23	17	6	2.8:1
Massive Hemorrhage Cases (with recovery)	Conservative	7	5	2	2.5:1
Massive Hemorrhage Cases (with recovery)	Surgical	11	8	3	2.6:1
Massive Hemorrhage Cases (fatal)	Conservative	5	4	1	4:1

Of the 59 cases of moderate and massive bleeding there were 45 males and 14 females—a proportion of 3 to 1.

Of the 23 cases of massive hemorrhage there were 17 males and 6 females—a proportion of 2.8 to 1.

Of the 7 cases of massive hemorrhage which recovered under conservative treatment there were 5 males and 2 females—a proportion of 2.5 to 1.

Of the 11 cases of massive hemorrhage who required surgery there were 8 males and 3 females—a proportion of 2.6 to 1.

Of the massive hemorrhage cases who died there were 4 males and 1 female—a proportion of 4 to 1.

From these figures one is able to state that severe bleeding is as likely to occur in the female as the male and that the course of treatment cannot be influenced by the sex of the patient.

#### OPERATIVE PROCEDURE

The operative procedure used in our 11 cases was subtotal gastrectomy, the ulcer being removed wherever feasible. When removal of the ulcer was not feasible the duodenum was transected distal to and around the ulcer and the closed duodenum was sutured around the ulcer center. In the present era of improved anesthesia and adequate blood replacement subtotal gastrectomy may be accomplished in every case and this is the practice of most surgeons. It is also the present day policy of most surgeons to perform a subtotal resection of the stomach even if an obvious ulcer is not palpated or visualized. This attitude presupposes that reasonable judgment has been employed to localize the bleeders to either the stomach or duodenum and that an overlooked case of esophageal varices is not discovered on opening the abdomen. It has been our experience that some of the severest cases of bleeding have arisen from acute erosions of the stomach—the stomach and duodenum appearing entirely normal to inspection and palpation.

It has been my purpose in this paper to show:

1. That bleeding ulcers have a definite mortality rate.
2. That the variance in mortality rates in different series of bleeding ulcer cases depends upon the type of bleeding cases included and reported in these series.
3. That a true appraisal of the importance of bleeding in peptic ulcer cases can be achieved by a comparison of series that contain the massive or severe bleeders only.
4. That the mortality rate in massive bleeding cases is approximately 20 per cent.
5. That only the massive bleeders produce the fatalities and that the mild or moderate bleeders are never surgical problems.
6. That only the massive bleeders that show a tendency to exsanguinate are candidates for surgery.
7. That criteria can be set up that will serve as yardsticks to determine which of the massive bleeders are potential exsanguinators.
8. That surgery during the bleeding phase should be done on those potential exsanguinators.
9. That surgery performed during the bleeding phase carries a reasonably low mortality.

10. That age and sex are not factors, per se, in influencing the operative indications.

11. That it is the duty of every internist and surgeon to attempt to reduce the mortality of the massive bleeding peptic ulcer case by the satisfactory methods he now has available to him—namely early gastric surgery during the bleeding phase in the case that is likely to exsanguinate.

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#### DISCUSSION

*Dr. A. Allen Goldbloom (New York, N. Y.):*—I gather you said regardless whether young or old, those with hemorrhage come to intervention. Is that true? You said something about individual shock. It does not respond to the conservative type of therapy, and within a certain length of time an individual sixty years of age, with the first hemorrhage, had to be operated upon, contrasted to young individuals having two or three hemorrhages. I believe this to mean that the young individual with the first hemorrhage who does not make the proper response at this time should have intervention. Are hemoglobin and red blood cells the only laboratory criteria? We do get, in cases of shock, severe hemorrhage. Are hematocrits determined then?

Also, I should like to know is there a time limit on this in the number of transfusions given to these patients.

*Dr. Gordon:*—Dr. Goldbloom asked about surgical intervention in a case of massive hemorrhage in a young individual without a history of previous episodes of bleeding. I would like to emphasize here that the indications for surgical intervention should not be influenced by the age, sex or previous episodes of bleeding but must rest solely on the condition of the patient and on

the criteria I have set forth in this paper. In answer to your question on laboratory data, I would like to state that that data which has been most useful to us has been the red blood cell count, hemoglobin and hematocrit values. The hematocrit readings have closely followed the red and hemoglobin values and have been omitted from this report for the sake of brevity. We are of the opinion that blood volume studies would have been of considerable aid and many clinics are employing these studies routinely. The question of the number of transfusions to be used before conservative treatment is abandoned may be restated in the following manner: if the patient who is bleeding requires 1,500-2,000 c.c. of blood per diem to maintain stabilization, he is a candidate for surgery. If the patient who has bled massively cannot be stabilized even with transfusions up to 5,000 c.c. within a period of less than 24 hours, he is a candidate for immediate surgery. If, however, stabilization is achieved he is not a candidate for surgery unless he then falls into the category of those patients requiring 1,500-2,000 c.c. of blood daily over a period of several days to maintain stabilization.

I would like to emphasize, at this time, that those cases in which the massive bleeding has been arrested, as judged by clinical and laboratory data, and in whom a fresh recurrence of bleeding presents itself within several days after the initial episode may become sudden fatalities even after the appearance of only a moderate hemorrhage of 300-500 c.c. of blood. Operation must be performed soon after the appearance of a recurrent hemorrhage.

## CHOLINERGIC BLOCKING AGENTS ON THE GASTROINTESTINAL TRACT\*

JOHN C. KRANTZ, JR., Ph.D.

Baltimore, Md.

The movements of the gastrointestinal tract have been, since antiquity, a source of interest and curiosity to man. The writhing entrails of animals were employed by ancient Greek and Roman priests as oracles by which omens for the future could be divined. With the advent of modern physiology and pharmacology the movements of the gastrointestinal tract have been the subject of most extensive investigations. In the main, these investigations have sought to unravel the mystery of intestinal movement which involves the very complex problem of smooth muscle tone and contraction. In addition, by various technics the action of drugs upon these movements have been studied for the purpose of providing better antispasmodic agents that are useful in the treatment of the many conditions of intestinal hypermotility. Much has been achieved but yet many fundamental questions await answering.

### THE ORIGIN OF INTESTINAL MOTILITY

The rhythmic contractions of the small intestine, segmenting and pendular, are myogenic in character. They are not dependent upon the rhythmic property of the smooth muscle itself. These activities are not abolished by the ganglionic poison nicotine nor by the local anesthetic cocaine. Peristaltic movements, however, are dependent upon the intrinsic nerve plexuses. The activity depends upon the innervation of the smooth muscle by the vagus nerve and its neurohormone acetylcholine. The reciprocating action of the sympathetic innervation with its neurohormones epinephrine and norepinephrine opposes the peristaltic movements. The vagal innervation of the small intestine extends into the large intestine to about one-half the distance of the transverse colon. The remainder of the colon and the rectum receive their innervation through the pelvic nerves from the second, third and fourth sacral segments. These pelvic nerves are cholinergic.

Hypermotility of the intestine is augmented by those agents which emulate the action of acetylcholine. It is accordingly blocked by those agents which antagonize or block the action of acetylcholine and other cholinergic agents.

### SITE OF ACTION OF ACETYLCHOLINE

The site of action of drugs which stimulate intestinal activity has long been the subject of controversy. It now appears that the action might occur in the ganglion and in the effector cells in the muscle wall or at the two loci simul-

\*Read before the First Annual Convention of the American College of Gastroenterology, Washington, D. C., 25, 26, 27 October 1954.

taneously. For example, Ambache (1949) found that when the autonomic ganglia of the intestine are poisoned with nicotine it required from ten to one hundred times as much acetylcholine to produce intestinal contraction as it did in the nonnicotinized intestine. He concluded that acetylcholine acted (1) at the effector mechanism in the smooth muscle, and (2) also by stimulating the ganglion to release more acetylcholine at this former site. Histamine and barium ions, on the other hand, were equally as effective in producing intestinal contractions after nicotine as in the nonnicotinized intestine. In therapy the problem of reducing intestinal motility resolves itself mainly into one of blocking acetylcholine. Hence the widespread use of cholinergic blocking agents, first at the effector mechanism alone and more recently at the vagal ganglion also.

#### THEORETICAL CONSIDERATIONS OF CHOLINERGIC BLOCKADE

It has been pointed out by Pfeiffer (1948) that the potent cholinergic drugs contain three prosthetic groups separated by optimal distances in the molecule. Smooth muscle cell activity is likely due to the anchoring of these groups on cell receptors. The acetylcholine molecule contains as its prosthetic groups (1) a ketone oxygen with a methyl group attached, (2) an ether group with a methyl group attached, and (3) a substituted quaternary nitrogen atom. These groups are common to many of the cholinergic drugs. Choline lacks the ketone oxygen group and hence contains only two prosthetic groups in the molecule. Its cholinergic activity is only negligible compared to acetylcholine. Indeed such a molecule as that of pilocarpine appears to possess three such prosthetic groups at the proper intramolecular spacing.

The potent blocking agents of acetylcholine, such as atropine, likewise contain three prosthetic groups at approximately the same intramolecular spacing. In these compounds the prosthetic groups are "contained in the center ridge of a large umbrella-like molecule". Pfeiffer's concept holds that these blocking molecules adhere to the cell surface by means of their three prosthetic groups. They block, by virtue of their "umbrella effect", the contact with the cell receptors by the prosthetic groups of the smaller cholinergic type molecules. They degrade slowly. Indeed through atomic forces exhibited by the blocking molecule other cell receptors may be found unavailable to the prosthetic groups of other impinging cholinergic molecules. Thus blockade is effected.

This theory gives an interesting schematic concept of cholinergic blockade which may be found applicable to other types of inhibition of physiologic activity by pharmacologic agents. It reminds one of the Ehrlich concept of cell receptors and drug action.

#### BELLADONNA AND ATROPINE

Long before acetylcholine was isolated by Hunt in 1907 the vegetable drug belladonna occupied a place of prominence in the physician's armamentarium.

Belladonna leaves are obtained from the *Atropa belladonna* plant. It was named *Bella Donna*, beautiful woman, because of the use of the drug by the female to produce mydriasis for cosmetic purposes. Owing to its poisonous nature Linneaus called it *Atropa* after Atrops, the eldest of the three Fates, the one responsible for the cutting of the "thread of life". The local action of the drug in the eye, producing mydriasis, was discovered accidentally by Daries (1776), a drug clerk of Hamburg who inadvertently rubbed some of the extract into his eye.

The plant is a bushy perennial which grows to a height of 1 to 1.5 meters. The alkaloids are present in the root as well as the leaves. Formerly the root was also extensively used to make extractive preparations. The principal alkaloids of belladonna are: (1) atropine, (2) hyoscyamine, (3) scopolamine (hyoscine), and others of minor importance.

The most important alkaloid of belladonna is atropine. It probably does not preexist in the plant but is formed from its isomer hyoscyamine in the extraction process. Atropine is now prepared synthetically also.

The cholinergic nerves are motor and secretory to the stomach and motor to the intestines. Atropine affords an effective blockade. It will lessen the motor activity and tranquilize the hypermotility of an excessively active gastrointestinal tract. Sanozki in 1893 was probably the first to show that atropine inhibited not only gastric hypermotility but also the secretion of gastric juice. An important feature of the effect of atropine upon the gut is the absence of tolerance on the part of the patient even upon prolonged use.

Chapman, Rowlands and Jones (1950) studied the effect of various antispasmodics upon the motility of the upper portion of the small intestine in man. They made their recordings by means of a multiple-balloon water manometer system. The drugs were administered in the usual therapeutic doses. Atropine 0.45 to 0.6 mg., or 20 drops of belladonna tincture, produced a decrease in propulsive waves and total contractions 50 per cent greater than that obtained with placebos. These investigators found none of the synthetic antispasmodics tested equal in efficiency to the belladonna preparations. Pavatrine and Trasentin were among the commonly-used antispasmodics tested.

#### ATROPINE SUBSTITUTES

Through the years the organic chemist and pharmacologist have endeavored to produce atropine substitutes with a greater degree of specificity for the intestinal tract, thus eliminating some of the untoward side-effects of atropine. For example, Fromherz in 1937 produced Syntropan. Syntropan elicits about one-hundredth the mydriatic and antisialogogue action of atropine. On the gut, however, its antispasmodic action is about one-twentieth that of atropine. Syntropan has many competing synthetic atropine substitutes. Among these are

Homatropine Methylbromide, Trasentin, Pavatrine, and more recently Bentyl Hydrochloride and Pamine Bromide.

What then is the drug of choice as a simple intestinal cholinergic blocking agent? It appears to this observer that more patients are benefited for longer periods of time with atropine than with any of its substitutes. Therefore it should be considered first. If, however, results are not achieved it becomes a matter of fitting the synthetic substitute to the patient's needs with a minimal of side-effects. Not all patients will receive the same degree of relief of symptoms from the same antispasmodic.

#### CHOLINERGIC-GANGLIONIC BLOCKING AGENTS

It has been previously stated that acetylcholine acts at the autonomic ganglia as well as at the effector mechanism in the smooth muscle. To block more effectively the activity of acetylcholine, chemists sought to synthesize molecules which would block acetylcholine at each locus of action. Such a compound is Banthine, and more recently Pro-Banthine. Other agents of this series are Antrenyl, Prantal and Monodral. These molecules contain in addition to the cholinergic blocking portion of quaternary nitrogen atom responsible for autonomic ganglionic blockade. No one can doubt that these agents which doubly block the action of acetylcholine have been a distinct advance in anti-spasmodic therapy. Their widespread use and their effectiveness in cases which fail to respond to atropine bespeak their value.

Nevertheless the use of these agents poses some interesting questions. The ganglionic blockade if achieved is not specific for parasympathetic nerves. Sympathetic ganglia will be also blocked, thus diminishing the output of epinephrine and norepinephrine at the myoneural junction of the sympathetic nerves to the intestines. Thus the tranquilizing effects of these neurohormones will be nullified. Furthermore, it has been seriously questioned whether ganglionic blockade can be actually achieved within the therapeutic dosage levels. There are many who hold that with these agents their effectiveness depends mainly upon cholinergic blockade.

From a clinical standpoint the danger of Banthine-type therapy lies in a false sense of security which it frequently gives the patient. At times drugs of this type will relieve pain when acid and irritation are still present. Almy states the case very cogently, "Banthine merely resists the storms of impulses over the autonomic system, but is not an impervious barrier to them."

#### SUMMARY

Napoleon once declared, "Dyspepsia is the end of all things, kingdoms, expeditions and the kings." Dr. George Crile spoke of peptic ulcer as "the wound stripe of civilization". Indeed since this malady and its sequelae involve nearly

10,000,000 Americans, the importance of this problem which we face in producing better therapeutic agents cannot be over-estimated. Fundamental knowledge has been increased, new antispasmodic agents are now playing a major role in making the ulcer patient's life more useful and enjoyable. The outlook for the future is bright as we begin to interpret motility and the antispasmodic action of drugs at an enzyme and even at a molecular level. The search is exciting and the stakes are high, for as Charles Darwin once wrote to his friend Hooker, "Adios, my dear Hooker; do be wise and good, and be careful of your stomach, within which, as I know full well, lie intellect, conscience, temper, and the affections."

# THE NONSURGICAL MORTALITY OF CARCINOMA OF THE STOMACH\*

## A PROBLEM OF RESPONSIBILITY

FREDERICK FITZHERBERT BOYCE, M.D.

New Orleans, La.

Carcinoma of the stomach has always been a tragic disease. The most tragic fact about it today is, as it has always been, that the mortality from it is overwhelmingly nonsurgical. Without surgery, and radical surgery at that, the course of all its victims is relentlessly downhill to the grave. That is still the fate of most of them, and of those who are operated on, less than half come to surgery when gastrectomy, even for palliative purposes, is still feasible.

In 1951 there were 23,683 deaths from carcinoma of the stomach in the United States<sup>1</sup>. In the same year, according to the Bureau of Census statistics, there were 4,500 deaths from gastric ulcer and well over 5,500 from secondary and unspecified neoplasms of the liver. A clinical surgeon would be fatuous indeed if he did not assume that a certain proportion of the deaths from gastric ulcer and a very large proportion of the deaths from neoplastic disease of the liver were also the result of carcinoma of the stomach.

Against this bleak and entirely realistic background the surgical results reported from such institutions as the Mayo Clinic, the Lahey Clinic and similar highly organized, brilliantly staffed services fall into their proper perspective. For one thing, these results are being accomplished in a selectivity of hospital population which in itself makes the picture totally unrepresentative. For another, while they are the best results being achieved today, they are not really very good. When they are viewed against the nonsurgical mortality in carcinoma of the stomach, it becomes evident how far we still are from the solution of this particular medical problem.

### THE FACTS OF GASTRIC CANCER IN A LARGE GENERAL HOSPITAL

In preparation for the presentation of this paper I reviewed my own previous studies of carcinoma of the stomach at Charity Hospital of Louisiana at New Orleans<sup>2-5</sup>. Before discussing them, and the additional study which I have just completed, let me fill in the background. This hospital now has more than 3,000 beds. Last year it admitted 66,000 patients. During the 22-year period covered by my studies it has admitted more than 1,125,000 patients. No hospital in the country has anything like its Negro population. When I first began to study carcinoma of the stomach there, the admissions were approximately 45:55

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From the Department of Surgery of the Tulane University of Louisiana School of Medicine

in favor of white patients. The balance has gradually shifted over the years, and in 1952 and 1953 the admissions ran approximately 69:31 in favor of Negroes.

This hospital is a world removed from such an institution as the Mayo Clinic, for instance. In many respects its population represents the medical flotsam and jetsam of the city and adjacent portions of the state. Its patients represent the lowest level of financial incapacity. Frequently, though naturally not always, they also represent the lowest level of intelligence and hygienic living. The Negro element would often be incomprehensible to those not called upon to deal with it regularly. Even in these days, when their financial and social status is so vastly improved, Negroes are inclined to be careless of their health, and they are notoriously indifferent to early signs of illness, especially if they are not associated with acute pain.

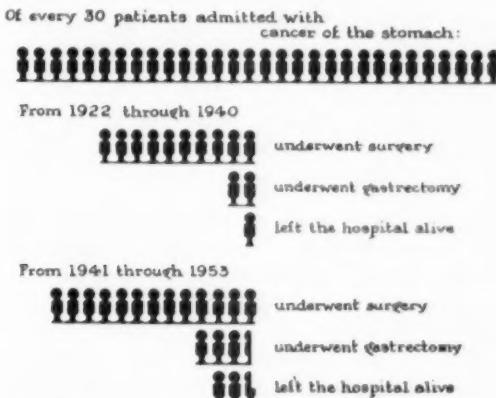


Fig. 1—Carcinoma of the stomach, Charity Hospital of Louisiana at New Orleans. The total picture, 1922-1953.

Charity Hospital is a teaching hospital. The best trained and most experienced surgeons in the community are therefore on its staff. It also has a non-teaching section. A great deal of the surgery is done, of course under supervision, by residents in training. The hospital therefore represents a cross section of surgical skill and practice, just as its population represents a section of the population not encountered in the clinics and hospitals in which the best results in carcinoma of the stomach are being achieved. Reports from it present a much truer picture of this disease than results which paint a more hopeful picture. This situation is likely, I fear, to continue, even when the full truth about carcinoma of the stomach is known and we can proceed in the light of full knowledge whereas now we walk in the dark.

Three of the four previous studies which I have made of carcinoma of the stomach at the New Orleans Charity Hospital were spot checks, so to speak, of

the surgical status of the disease. They were made in 1933, 1941 and 1952, and each of them was based on the 200 most recent surgical cases. The fourth report, which covered the period between 1926 and 1943 inclusive, consisted of 135 nonsurgical fatalities in which the diagnosis was confirmed by autopsy in the hospital or by the coroner. For the purposes of this presentation I have studied the additional 68 nonsurgical fatalities which occurred between 1944 and 1953 inclusive, so that this series now consists of 203 cases. All of these data I shall use not statistically but merely as a point of departure for this discussion.

In one respect it is a sound plan to discuss the mortality of carcinoma of the stomach only from the standpoint of confirmed cases. A totally incorrect impression is received, however, if the fatalities are excluded in which the diagnosis was made on radiologic, cytologic, or purely clinical grounds. These fatalities, as a matter of fact, comprise the bulk of the deaths. Let me give you, therefore, the whole picture at the New Orleans Charity Hospital during the 31 years over which these collective studies have been made (Figs. 1-4).

As you can see, there has been a considerable improvement in immediate results as time has passed. More patients have been submitted to surgery. More gastrectomies have been performed. The mortality of all surgery, and more particularly of gastrectomy, has materially decreased.

Can we take hope from these apparent improvements? Not as much, I am afraid, as a casual inspection of the figures might suggest. It is naturally a considerable advance that more patients are now being given whatever chance of life surgery holds for them, but that does not mean that the outlook, measured in terms of the stage of their disease when they are first seen, is much better for most of these patients. The number of gastrectomies has not been greatly increased by any improvement from that direction. On the contrary, the increase has come from (1) a commendably bolder and more aggressive approach to the disease as a whole; (2) by an extension of indications for resection, an extension which was sometimes, perhaps, overgenerous and which, perhaps, explains a certain amount of the postoperative mortality; and (3) by the present general and wise tendency to substitute gastrectomy for gastroenterostomy as a palliative procedure.

Just over half of the operations in the last 200 surgical cases studied were resections, but considerably less than half of the resections were undertaken with any real hope of cure. The improvement in the immediate mortality—I am not dealing with end-results in this paper—is easily explained. To some degree it is due to improved surgical technic and to better judgment. It is chiefly due, however, to newer methods of anesthesia, to more competent administration of anesthesia, to better preoperative and postoperative care, and to a general use of adjunct measures, particularly constant intestinal decompression, the maintenance of a physiologic fluid balance, the liberal use of whole blood, and the availability of the antibiotics.

For my own part, the chief cause of optimism in the present situation is derived, paradoxically, from the last 68 nonsurgical fatalities analyzed. On the surface, a series of fatalities does not seem particularly encouraging. They supply cold comfort, I grant, but they are nonetheless encouraging.

In my 1944 study of the nonsurgical mortality of carcinoma of the stomach at the New Orleans Charity Hospital there were 28 cases, in a total of 135, in which postmortem examination indicated that resection, in spite of local extensions and metastases, seemed well within the possibilities of modern technics. There were a number of propitious circumstances. In almost a third of the 28 cases the growth was prepyloric and therefore in the most favorable of all locations for resection. There was no instance of carcinoma at the cardia, which is the most unfavorable of all locations. It is true that the neoplasms were sometimes quite large, but mere bulk is no contraindication to gastrectomy. The patients were usually in poor condition, or had other organic diseases, but vigorous efforts at preparation might conceivably have transformed them into better surgical risks.

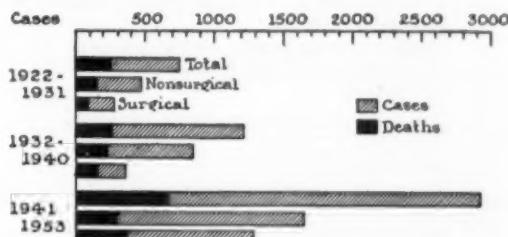


Fig. 2—Carcinoma of the stomach, Charity Hospital of Louisiana at New Orleans. The changing picture, 1922-1953.

With only 2 exceptions these 28 patients had been admitted to medical services in the hospital, a practice which W. J. Mayo<sup>6</sup> was inveighing against almost 50 years ago but which still continues. Twelve died of various causes shortly after admission. Only 1 of the 12 had had any previous medical treatment and the profession, therefore, had no responsibility for their deaths except in the most general sense. The other 16 had previously been treated by private physicians, or in the hospital clinics and wards, for peptic ulcer and other digestive disturbances or for other symptoms which, in the light of after events, might well have been the first manifestations of gastric carcinoma, or they had been under observation for other, unrelated diseases.

Since these 16 patients were on medical wards, the internists, perhaps, must carry most of the responsibility for them. But we who are surgeons can take no pride in what happened to at least 7 of them. Surgical consultation was requested in each of these cases but operation was not recommended in any of them. In 1 case it was suggested that surgery be reconsidered after the effect

of antisiphilitic therapy had been observed. In 1 case the risk of surgery in a 71-year old cardiac was regarded as too great. In 2 cases jejunostomy was proposed but the patients wisely declined this counsel of desperation. In the 3 remaining cases the malignancy was thought to be inoperable.

There are two important considerations in these potentially resectable cases: 1. In none of them was a really vigorous effort made to improve the patients' condition to the point where surgery might have been possible. 2. In each of the 7 cases in which surgical consultation was requested and in which the surgeon was given the chance for which he is constantly pleading—and for lack of which he consistently berates the internist—the condition was either misdiagnosed altogether or the status of the growth was misinterpreted.

My reason for deriving modified optimism from my analysis of the most recent nonsurgical fatalities at the New Orleans Charity Hospital is that none

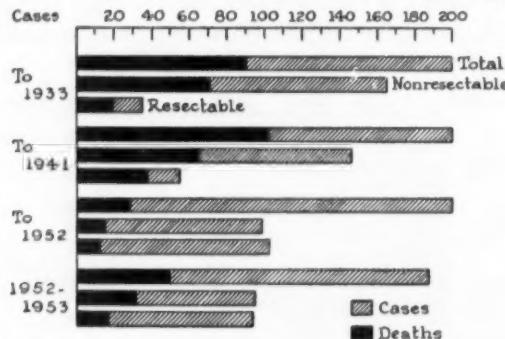


Fig. 3—Carcinoma of the stomach, Charity Hospital of Louisiana at New Orleans. The first three sets of bars represent the distribution of cases according to resectability and mortality in three separate series analyzed in detail between 1933 and 1952. The fourth set of bars presents the recorded hospital cases for 1952-1953; this series has not been analyzed in detail.

of these things happened in them. Six of the 68 patients refused surgery and 2 refused even roentgenologic examination but there was no instance in which a surgeon, called in consultation, failed to recommend surgery for a growth which autopsy showed to be resectable. Vigorous, though unavailing, efforts were made to get a number of patients into condition for surgery. One man was actually taken to the operating room, but he reacted so badly to the anesthetic that it was decided that he could not tolerate surgery. The decision was probably correct, as he died 10 days later. There were only 3 patients in the series with resectable growths. Two of them died suddenly, one of coronary occlusion and the other of a cerebrovascular accident. The third patient died of burns.

This is, of course, a sad way to measure improvement, but improvement of a sort it is. The way to further improvement, in fact, is along the same thorny path. We must be careful that we do not turn backward on it.

## CURRENT TRENDS IN THE LITERATURE OF GASTRIC CANCER

In preparation for this presentation I also read comprehensively in the recent literature on carcinoma of the stomach. My survey left me with the conviction that in the over-all clinical concept of this disease we have yet to improve upon what the older physicians—Osler, Moynihan, Welch and the Mayos, among others—had to say about it. It also left me with the conviction that if we set our course by some of the recent literature, our patients will be the worse for it.

The depressing fact has long been recognized that each cancer of the stomach, at its inception, contains within itself the seeds of the patient's fate. This factor, which is now termed biologic predeterminism<sup>7,8</sup>, cannot be gainsaid or controverted. The most depressing consideration, however, is not the *fact* of biologic predeterminism but the recent tendency to advocate it as a guide to

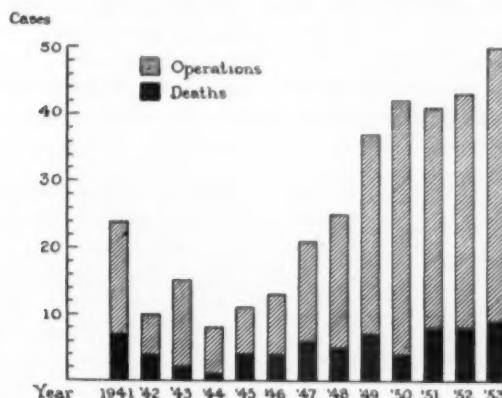


Fig. 4—Carcinoma of the stomach, Charity Hospital of Louisiana at New Orleans. Distribution and mortality of gastrectomy, 1941-1953.

prognosis and therefore to therapy. Carried to its ultimate conclusion, this concept engenders a spirit of defeatism which would bring to naught the only policy which has ever accomplished any results in this disease, the policy of making do, so to speak, with what is available. That means bringing the patient with suspected carcinoma of the stomach to the surgeon as promptly as he can be brought.

The premises of the theory of biologic predeterminism and their implications are about as follows:

1. The undue emphasis put upon the importance of early treatment ignores the complex biologic nature of cancer, as well as the wide disparity of behavior of the disease in its variable forms and sites of origin.

2. Rigid ideas of prognosis in terms of duration of symptoms and dimension of lesions should be abandoned in favor of an attempt to evaluate the biologic potential of a neoplasm in an individual host.
3. Much of the time and effort expended in radical treatment of cancer is wasted on lesions predestined at their biologic inception to be lethal.
4. To no small extent, the doctrine of the synonymy of early treatment and curability should be recognized for the useless shibboleth it is.

This is not a philosophy which most surgeons would be willing to accept. It is a frank surrender to defeatism. It is a sure means of increasing the non-surgical mortality of the disease. We have long realized that the most important consideration in the prognosis of carcinoma of the stomach is the biologic nature of the growth. We know only too well that in the "most lethal pattern" of the disease the patient is dead almost before he has a chance to temporize. We are perfectly aware of the long silent or latent period between the incipiency of the growth and its first clinical manifestations. It is undoubtedly true that for all practical purposes it is only by the sheerest accident that most of the cases of carcinoma which are seen early come to the attention of the surgeon in that stage.

I cannot see, however, how any of these considerations would justify us in relaxing our efforts to save patients who might possibly be saved, no matter how few they may be and no matter how desperate their plight. In 1940, after Pack and Livingston<sup>9</sup> had analyzed the 14,000 gastrectomies reported in the world literature up to that date, they reached 65 conclusions. One of them was that for approximately 75 per cent of patients with this disease surgery does not hold out the faintest hope of cure. I greatly fear that this conclusion still holds. But I am also certain that the first of their conclusions is still correct. It was that carcinoma of the stomach is curable.

This is, of course, not the first time a philosophy that amounts to defeatism has been advanced in carcinoma of the stomach. A number of years ago Schindler<sup>10</sup> proposed that the operability of a given case should be determined by the outcome of gastroscopy and roentgenologic examination and that the prognosis should be based upon histologic typing and the presence of metastases. Many a patient would lose his chance of cure if that policy became universal. Many a patient who is now relieved, at least temporarily, by palliative gastrectomy would die a more terrible death.

#### DIAGNOSTIC CONSIDERATIONS AND THE TIME LAG

In the doctrine of biologic predeterminism, the time lag is of little consequence. This philosophy, in fact, leads to the decidedly upside-down conclusion that the longer the history, the better are the patient's chances of survival. Most of us would prefer to put it that a patient with a long history

of symptoms probably has a neoplasm that grows slowly and is slow to metastasize, and that he is not necessarily doomed. These facts certainly do not mean that there should be any relaxation in our efforts to bring patient and surgeon together promptly. For one thing, regardless of its degree of malignancy, the earlier a growth can be removed, the simpler and less hazardous is the operation. For another, who is to decide the precise time at which even a slow-growing neoplasm becomes inoperable, as it inevitably will?

Over the years there has been, unfortunately, very little real improvement in the time at which the patient with carcinoma of the stomach comes to the surgeon. That is universally true. Part of the delay is caused by the patient himself. Part of it is caused by the physician whom he first consults. Part of it is caused by the hospital staff. There is not much, except educationally, that we can do about the patient's part in the delay. The remaining delays are the responsibility of the medical profession and we gain nothing by not facing that fact.

In the 203 nonsurgical fatalities at the New Orleans Charity Hospital 22 patients died too promptly for any sort of history to be obtained and the diagnosis had to be established at postmortem. In many of the remaining cases the histories were too inadequate to obtain many details from them. But it was still possible to determine that at least 30 patients had consulted one or more physicians at varying intervals of time after they became ill and that immediate hospitalization had been advised in only 6 instances. Three patients underwent roentgenologic studies but when the reports were negative, they, like the others, were treated with pills, powders, vitamins, antispasmodics, antibiotics, medication for anemia, and a variety of other measures, all of them symptomatic, which were instituted on incorrect diagnoses or no diagnosis at all. The situation in these nonsurgical fatalities precisely paralleled the situation in all the surgical series I have studied. In the last 200 cases, for instance, 129 patients had consulted one or more private physicians before they were hospitalized but only 16 were told to enter the hospital immediately for investigation and possible surgery. Surely the biologically predetermined character of the growth should not prevent us from taking vigorous steps to alter what is a universally erroneous policy.

As a general principle, it may be said that diagnostic difficulties in carcinoma of the stomach increase in exact proportion to the promptness with which patients seek medical aid. Early symptoms are important in the aggregate and eventually, but they are insignificant and misleading individually and presently except to the physician whose index of suspicion is consistently high. Digestive distress, which would seem logically to be the cardinal manifestation of a disease located in the stomach, may be entirely absent until the malignancy is far advanced. If it is present, it may be no more characteristic of carcinoma than of a dozen other diseases with gastric manifestations. The wide variety

of initial symptoms presented in these 203 nonsurgical fatalities, as in all series, is one explanation why many of the patients died without surgery. We shall not begin to save all the lives which can be saved in this disease until we force ourselves to bear in mind, day in and day out, that early, curable cancer of the stomach has no typical pattern and that the classical picture is the terminal picture.

Diagnostic investigation was entirely lacking or was incomplete in a number of these fatalities because the patients died so promptly or because they were in no condition to be investigated. The investigations which were carried out, however, deserve some comment. In a number of these cases, and in an even larger proportion of the surgical cases studied at Charity Hospital, the staff, in their commendable desire to make a precise diagnosis, sometimes displayed what seemed a tendency to study the patients to death, particularly from the point of view of the laboratory. Although investigation in some cases was perfunctory, usually, when circumstances permitted, it was exhaustive, and sometimes it was too exhaustive for the patient's good. One reason for the poor results in carcinoma of the stomach is failure to remember that it is a very urgent disease.

The analysis of these 203 nonsurgical fatalities, together with the earlier analyses of 600 surgical cases, makes a number of points clear:

1. Gastric analysis is not a reliable diagnostic test, nor is it a very helpful one. When hypoacidity or anacidity is present, gastric carcinoma is a more likely possibility, but the diagnosis is not excluded by either normal levels or high acidity.
2. Gastroscopy is a useful adjunct measure when it is positive, but it is no more than that. A negative report must not be relied upon. Often a negative report merely means that the neoplasm is in an area of the stomach which cannot be visualized. A positive biopsy is conclusive proof of cancer, but a negative biopsy does not differentiate between ulcer and cancer, no matter how well the lesion is visualized. These remarks about gastroscopy are chiefly based upon the results in the surgical series, in which it was widely used. It was performed in only 5 of the nonsurgical cases, all in the most recent series. It was usually omitted because the patients were too ill to tolerate what is, after all, still something of an ordeal, or because carcinoma of the stomach was not suspected.
3. Cytologic studies were not used in the first series of nonsurgical fatalities because the method had not yet come into use. The technic was used 8 times in the 68 cases which made up the second series, in all instances on pleural and ascitic fluid. The fact that the tests were positive in 5 cases carries its own implications as to the status of these patients. Treatment in 22 of the 68 cases, in fact, consisted only of paracentesis and in 2 others of thoracentesis. The surgical cases studied show that if cytologic examination of the gastric secretion is positive, this is a useful confirmatory method or an absolute diagnostic method,

certainly absolute enough to warrant immediate exploration. If the examination is negative, it is of no help whatsoever, and no great amount of time should be spent trying to obtain positive results.

4. Next to a well taken and carefully interpreted history, roentgenologic examination is the most useful diagnostic method in carcinoma of the stomach. Clinical suspicion and radiologic evidence are responsible for the majority of correct diagnoses, though the high percentage of correct radiologic diagnoses in these nonsurgical cases is, as always, an index of the large proportion of advanced cases. The chief risk in radiologic examination—and a risk it is—is the clinician's habit of letting the roentgenologist do his thinking for him and of basing his therapeutic course upon what the roentgenogram does, and, more particularly, does not reveal. I doubt that a decision as to operability or inoperability of a growth in the stomach should ever be made on the basis of roentgenologic findings alone. I am quite sure that if they are not in accord with clinical suspicion, they should be ignored.

#### CARCINOMA OF THE STOMACH AND GASTRIC ULCER

On one point I am in complete agreement with the proponents of biologic predeterminism in cancer of the stomach, that the widest field of improvement in gastric cancer lies in the prompt resection of all gastric ulcers. In every series of gastric cancers that has been studied from the New Orleans Charity Hospital, the ulcer-cancer question has arisen in a quarter or more of all cases. Walters<sup>11</sup>, in 1945, wrote that at the Mayo Clinic "the most disastrous observation" in regard to the symptomatology of gastric cancer was that 30 per cent of the patients had an ulcer history. The radiologist had made the diagnosis of ulcer, he went on, in 10 per cent of the cases submitted to resection, and 80 per cent of the patients with gastric cancer who had been treated for ulcer had responded favorably. What has well been termed "treatment by appeasement" has many arguments against it. The most cogent is that the regimen of medical therapy for gastric ulcer consists of precisely the measures which will control, at least temporarily, an ulcerating carcinoma. The danger is even greater now that the effectiveness of Banthine has been established and operations on the vagus nerve are becoming popular.

The most devastating account which has ever been published of the dangers of medical treatment of gastric ulcer is by Cain, Jordan, Comfort and Gray<sup>12</sup>, from the Mayo Clinic, in 1952. It is a 5-year follow-up of 414 patients with small gastric ulcers who were treated medically. Seventy-eight had refused surgery. In the other 336 cases the choice of medical therapy was deliberate.

Only 85 of the 414 patients had complete and permanent relief by medical measures. Twenty died of causes unrelated to gastric disease during the 5-year period of observation. One hundred forty subsequently required operation because of failure to obtain relief; 34 of this group were found to have gastric

carcinoma, which in 9 cases was not resectable. Nine other patients who were not operated on eventually died of cancer of the stomach. In these 43 cases the malignant disease became evident at periods varying from less than a month to more than 5 years after medical treatment had been decided upon. When cancer appeared promptly, or within a year or two, it was undoubtedly present when the decision was made to follow nonsurgical therapy. When it appeared after an interval of several years, it was probably a new development. In any event, as these figures show, the physician who elects to treat a patient with a presumed gastric ulcer by medical means can give him no real assurance that he does not have cancer or that cancer will not develop later. These figures also suggest that in all fairness the physician should also inform the patient that the risk of surgery for gastric ulcer, which is about 2 per cent, is a good deal less than the risk of the presence of malignant disease or of its development in an ulcer-bearing stomach, which is about 10 per cent.

The x-ray cannot distinguish between ulcer and cancer. Even if the ulcer is apparently healing, the impression may be incorrect; the healing process may prove to be an ulcer crater filled with malignant cells. Cole<sup>13</sup>, in 1929, spoke with a high degree of scorn of the roentgenologists who were reporting, "This patient has a gastric lesion the nature of which can be determined only by exploration." We should be saving more lives from carcinoma of the stomach if roentgenologists would continue to write such reports and if internists and surgeons would heed the warning.

Much of the discussion of ulcer-cancer is as useless and futile as it is acrimonious. Some pathologists believe that the transition from a benign to a malignant ulcer never occurs. Some believe that it does. The original estimates of the transition were certainly too high. But none of these things make any real difference. In these 203 fatal cases there were only 3 instances in which the pathologists thought that a benign ulcer might have undergone malignant change. There were, however, some 50 patients who presented the symptoms and signs, including the x-ray evidence, of a gastric ulcer. Many of them had been treated for gastric ulcer and they lost their lives as a result. In spite of the apparent irrefutability of the clinical, radiologic and laboratory evidence of gastric ulcer, they proved the fallibility of all the evidence by dying of cancer. When and how malignancy originates in an ulcer-bearing stomach may be of academic interest. The clinician is concerned with graver matters: When he encounters an ulcerating lesion of the stomach, he may be dealing with cancer, and the patient will lose his life if his guess, however informed and well-intentioned it may be, is wrong.

#### MISSSED OPPORTUNITIES IN GASTRIC CANCER

In a number of these nonsurgical deaths, just as in many of the surgical cases which I have studied, carcinoma of the stomach was overlooked for a long time or the opportunity to diagnose it was missed altogether.

In some cases it developed in association with other diseases. Like all cancers, cancer of the stomach is most frequent in the age period when chronic illness is most frequent, though I hasten to add that it is by no means confined to this period of life. In such cases its manifestations are often overshadowed by the manifestations of chronic illness, or are interpreted as a new phase of a longstanding illness. This is a state of affairs which is likely to increase in importance as more and more persons live into the older age groups. It is a possibility which directors of homes for the aged and of institutions for the custodial care of patients with chronic illness should be warned against and should take to heart. Two of the patients in the last nonsurgical series were admitted from such institutions almost moribund because their lethal illness had been completely submerged in complaints attributed to their age and their chronic diseases.

Many of the patients in both the nonsurgical and the surgical series studied at Charity Hospital had been coming to the clinics or had been hospitalized at intervals during the months and sometimes the years before their final admissions. A number of them had undergone surgery for other conditions, including cataracts, hernia, so-called chronic appendicitis, and prostatic disease, which in 2 instances was malignant. It is always interesting, and it is frequently depressing, to re-examine the old records in such cases. Many times, sometimes weeks and months earlier, there will be found a casual hint or a clearcut indication of symptoms referable to the gastrointestinal tract or of other symptoms which were ignored by the specialists concerned with another field until it was too late.

These cases all represent missed opportunities. They are instances of gastric cancer which develops under medical observation. They also carry their own lessons. The first is that patients in middle life and beyond, regardless of the origin of the complaints which they regard as most important, must not be dismissed from observation until all their symptoms have been investigated. The second lesson is the wide field of case-finding in cancer open to all physicians. If all of us, specialists as well as general practitioners, regardless of our special interest, did no more than inquire into the digestive mechanism and general health of all our patients, and if we listened to the replies and acted upon them, a very large number of carcinomas of the stomach would thus be identified, and some of them, at least, would be early, curable cases.

As to mass case-finding, the proponents of biologic predeterminism are correct in their statement that no method has proved of any real value. Certain cytologic studies, photofluorography, and even cancer detection clinics have failed. My own feeling is that no method will prove of value until some biologic test, such as the Wassermann reaction, is devised to identify early cancer, before it becomes clinically evident.

Since the mass screening of all persons with possible early carcinoma of the stomach is obviously impractical, again we must make do with what we have. That means, in practice, the screening of selected groups. Patients in whom anacidity is detected, for instance, are candidates for suspicion. They must be kept under careful observation and re-studied at 6-month intervals, at least. The method of gastric analysis without intubation described by Sharp and Hazlet<sup>14</sup> may make the average patient more willing to be re-observed than he is likely to be with present technics.

The connection of carcinoma of the stomach with pernicious anemia is now clearly established, although the link between the two diseases remains to be found. The association is far more than could be expected to occur by chance. Now that patients with pernicious anemia, thanks to modern methods of therapy, are living into the cancer age, they form another group of persons who must be re-investigated at regular intervals.

When gastric polyps, which are frequently associated with pernicious anemia, are detected, observation is not enough. They should be promptly removed. Exactly what proportion of these polyps become malignant it is not possible to say; in reported series it ranges from 10 per cent to 50 per cent or more. The proportion makes little difference. The situation is precisely what it is in gastric ulcer: Radiologists cannot distinguish benign from malignant growths. The most astute and most experienced clinician cannot make the distinction or predict the future course in any given case. Some observers feel so strongly about the dangerous potentialities of gastric polyps that they consider total gastrectomy justified when they are diffuse. Be this as it may, the physician who allows a patient with a gastric polyp to retain it with his acquiescence is taking unwarranted chances with a human life.

#### THE DIAGNOSTIC VALUE OF EXPLORATORY LAPAROTOMY

My own feeling is that if the diagnosis of gastric cancer seems clearcut in the light of the history and roentgenologic evidence, confirmation by gastric analyses, cytologic studies and gastroscopic examination is not necessary. If the reports confirmed the diagnosis, my planned course would not be altered. If they did not, and if I continued to think the diagnosis reasonably certain or even remotely probable, I should still advise exploration. Similarly, if the disease could not be positively excluded after adequate—and prompt—investigation by all available methods, the next step would be to prepare the patient for exploration.

Some of the recent literature suggests that this is a rather reckless point of view. I cannot agree. I am not advocating a resort to the knife before reasonable diagnostic efforts have been exhausted. On the whole, at the present time, exploratory laparotomy is used much later, and much less often, than it should be used. As to the argument that exploration is an admission of the inadequacy

of other diagnostic measures, I agree that it is, but I do not see that that makes it of less value or lessens, in any way, our obligation to use it until more efficient diagnostic measures are devised. Until we make exploration a part of our diagnostic routine, we shall not be doing the best that we can for patients with carcinoma of the stomach.

The mortality of exploratory laparotomy will continue high as long as it is used, as it most often is used now, as a last resort, in patients suffering from cachexia and inanition, who are not very far from death. Undoubtedly surgery hastens the fatal outcome in some such cases, though not by very much. The mortality will, however, immediately become negligible when exploration begins to be used, as it should be, as a diagnostic tool, in patients in whom the disease is only suspected and who are still good risks. If cancer is found and proves resectable, exploration can become resection. The best results in this disease are achieved in cases in which surgery is performed on suspicion rather than certainty of diagnosis. If the exploration is negative, the surgeon's course has still been correct and he has no reason for self-reproach.

#### TOTAL GASTRECTOMY

The advocates of biologic predeterminism conclude that this concept completely eliminates total gastrectomy. They may be right. This operation should certainly be limited to the cases in which the choice lies between total removal of the stomach and no surgery at all. As a routine, it is unthinkable. It would be morally indefensible to put all patients to an increased risk for the sake of one or two who might be saved by radical surgery. The end-results of partial gastrectomy may leave a good deal to be desired, but from every standpoint they are better, and they are accomplished with a far smaller risk, than the possible results of routine total gastrectomy.

Aside from these considerations, total gastrectomy should never be undertaken without due recollection of the fact that it involves a subsequent way of life, with dietary care and compensatory therapy, that is simply impossible in certain social and financial levels. A great many observers are now making the point that the remarkable reduction in mortality which has been brought about in total gastrectomy does not necessarily outweigh the unfavorable physiologic results which are produced in so many cases. The reservoir technics which have been devised may perhaps solve this particular problem. That is still to be seen. At any rate, before the operation is resorted to, the patient or his family should clearly understand what it implies and what are the alternatives to its performance.

Brunschwig<sup>18</sup>, who is the chief exponent of radical cancer surgery, states that the limits of operability have apparently been reached with resection of the entire stomach and adjacent viscera en masse. It is extremely doubtful that there is any justification, as he tentatively suggests, for wider resection of

smaller, apparently localized tumors than is now being practiced. The question here is not one of feasibility but of over-all accomplishment. It is unlikely that the greatly increased risk of such radical surgery could be justified by the possible improvement in end-results.

#### TERMINAL CARE

There is another phase of the therapy of carcinoma of the stomach which is inherent in the nonsurgical as well as the delayed surgical mortality. It concerns terminal care, and it is unfortunate that so little attention is paid to it in the literature and in teaching and practice. When it is obvious that nothing more can be done for the patient in terms of long survival, what is our professional responsibility? My own feeling is that he should be allowed to die, and to die in as much peace and comfort as possible. The physician should remember, as Cheever<sup>16</sup> once compassionately said, that he is the agent of relief, whichever way relief may come.

Dunphy<sup>17</sup>, in an excellent and equally compassionate discussion of this problem, points out that the surgeon has a moral obligation to see the case through one way or the other. In a well managed institution, as he says, the surgeon is always in the background as a strategist if not as a tactician. He has no right to drop the patient into the lap of the radiologist, the oncologist, or anybody else.

This does not mean, of course, that the physician is under any obligation to employ what Dunphy well calls "fantastic" measures to prolong life in the face of an intolerable and clearly terminal disease. I could not agree with him more completely. The administration of blood to these dying patients, for instance, is almost never justified. Eighteen of the 203 patients in the nonsurgical Charity Hospital series were transfused, sometimes several times, when their status was clearly terminal or almost terminal. In an occasional case it was thought that by some miracle the patient might be made into a suitable risk for surgery. In most instances the blood was ordered as a therapeutic gesture that was sometimes humanely inspired and was sometimes thoughtless and perfunctory, but that was usually as foolish and wasteful as it was futile.

One other point that Dunphy makes is usually overlooked: The support of the family is also the physician's obligation, since the crisis may be more terrible for them than it is for the dying patient. I can say from my own experience that I have no more grateful patients than those who come from the families in which I stood by the relatives as well as by the patients themselves until the end came.

#### CONCLUSION

The surgeon who writes of carcinoma of the stomach always finds himself saying the same things in conclusion. I am no exception in my self-plagiarism.

Pack and McNeer<sup>18</sup> once said that the management of carcinoma of the stomach is a philosophy quite as much as a technic, and that a surgeon had no right to treat the disease if his philosophy did not urge him to attempt the removal of every gastric cancer which he encountered. Everything I have said in this paper has been in support of that principle. This sort of thinking runs directly counter to the implications of the concept of biologic predeterminism. Unless, however, this sense of surgical responsibility becomes much more widely accepted than it is at present, we shall make little progress in the improvement of our results. No physician has a right to treat a patient with possible carcinoma of the stomach unless he is surgically minded and unless he intends to refer him, even on mere suspicion, to a surgeon. It would be even better if he called the surgeon into the case as soon as the suspicion arose. This is often a difficult disease to diagnose. Two heads are better than one. A joint study is less wasteful of time, effort and money, it is far easier for the patient, and it is usually far more effective, than two consecutive studies.

The clue to the management of carcinoma of the stomach in the light of present knowledge, which is all we have to go by, was stated 70 years ago by W. H. Welch<sup>19</sup>, who was not a surgeon but a very great pathologist: "The opinion entertained by the physician as to the propriety of surgical interference in gastric carcinoma is not a matter of indifference, for cases of gastric cancer come first into the hands of the physician and generally only by his recommendation into those of the surgeon." As to the rest of our responsibility for the patient, it is inherent in the inscription over the entrance of the cancer wing of the Middlesex Hospital, "until he is relieved by Art or released by Death".

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## CARCINOMA OF THE CECUM\*

### CLINICAL ANALYSIS OF 33 CASES

ROBERT C. LYNCH, M.D.†

New Orleans, La.

SAM B. HUTTON, M.D.

Dallas, Texas

and

GALE D. JOHNSON, M.D.

Dunn, N. C.

The insidious onset of carcinoma of the cecum frequently is used as a classic example of the silent, almost stealthy, development of carcinoma in the human body. The triad of anemia, loss of weight, and a mass in the right lower quadrant of the abdomen is not accepted at present as a criterion for early diagnosis of cecal carcinoma. By discarding this "classic triad", however, we are apparently left without other indications for suspecting the proper diagnosis strongly enough to establish it definitely. This study was undertaken to evaluate our own experience with this disease in an attempt to elucidate early diagnostic features.

### MATERIAL

During the ten-year period ending Dec. 31, 1952, of 125,000 new patients admitted to the Ochsner Clinic for examination there were 33 with proved carcinoma of the cecum, or an incidence of 0.0264 per cent. This probably represents a slightly higher incidence than usual because the majority of patients admitted to the clinic are referred from other communities.

### INCIDENCE ACCORDING TO SEX AND AGE

The sex distribution of reported series of cecal carcinoma is approximately equal. Although our series is too small to be conclusive, it showed a slight preponderance of males. As in cancer generally, carcinoma of the cecum in the present series was found to be more common among patients in the fifth, sixth and seventh decades of life. The disease has been reported in persons less than 30 years of age (1-3), although none of the patients in our series were that young. Only 2 of our patients (6.06 per cent) were under 40 years of age, but in large series (1-3) from 5 to 10 per cent are reported to be less than 30 years of age.

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†From the Departments of Surgery, Ochsner Clinic and Tulane University of Louisiana, School of Medicine, New Orleans, La.

The distribution of our cases according to age and sex is of interest. As will be noted in Figure 1, all but one of the patients between 30 and 60 years of age were men, whereas the majority of patients 60 years of age or older were women. Although the total number of patients is small, this fact would seem to indicate strongly that carcinoma of the cecum develops in men at an earlier age than in women.

#### SYMPTOMATOLOGY

Rankin and Johnston<sup>4</sup> have emphasized that patients with carcinoma of the cecum have one of three general groups of complaints. The largest group, those with "dyspeptic" symptoms, comprise 60 per cent of the patients seen. The second, or anemic group, accounts for 30 per cent, and the remaining 10 per cent complain primarily of an abdominal mass. These divisions are of help in recalling the symptoms of which the patient with cecal carcinoma may complain.

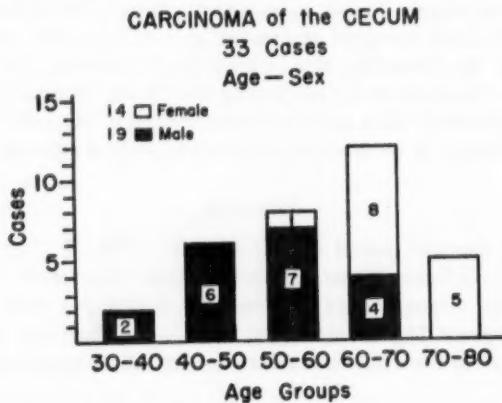


Fig. 1—Graphic distribution of 33 cases of carcinoma of the cecum according to age and sex.

Our cases were classified according to the patient's primary reason for seeking examination (Fig. 2). As might be anticipated, the largest number, or 14 patients (42.42 per cent) came to the physician because of pain. Eight patients (24.24 per cent) had noted a definite change in bowel habits, and 2 (6.06 per cent) complained of passage of blood from the lower bowel. In the remaining 9 patients (27.27 per cent), a group of symptoms, including the presence of an abdominal mass, was the reason for medical consultation.

Since patients rarely come to the physician with a specific complaint, it was thought that a more comprehensive view might be gained by aggregating the complaints of each patient. Thus, pain was a prominent symptom among 25 of the patients (Fig. 2). This varied from an aching, indefinite and intermittent discomfort to the severe colicky pain of intestinal obstruction. In one of the most

interesting cases, carcinoma of the cecum was discovered incidentally at the time of gastrectomy for intractable duodenal ulcer. During convalescence, nausea and severe pain, tenderness and rigidity developed in the right lower abdominal quadrant. At operation acute appendicitis due to obstruction of the appendiceal lumen from the cecal carcinoma was found. In other instances, the pain was explicable on the basis of obstruction, perforation or the reflex dyspeptic discomfort emphasized by Rankin and Johnston<sup>4</sup>.

The second most frequent symptom was unexplained loss of weight, which was noted by 23 patients (69.69 per cent). The amount lost varied from 5 to over 25 lbs., but in 9 of the 33 patients, the amount was over 25 lbs. This attains greater significance when it is realized that the average older individual often has difficulty in avoiding gaining weight on the average diet of today.

Seventeen patients (51.51 per cent) reported definite change in bowel habits (Table I). Diarrhea is generally considered to be the usual change in bowel

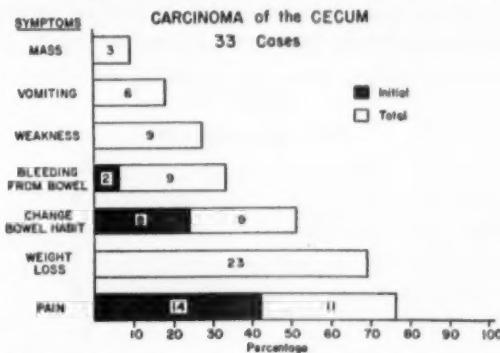


Fig. 2—Graphic distribution of 33 cases of carcinoma of the cecum according to chief complaint.

habit noted by patients with carcinoma of the cecum but this was not true among our patients. Six patients noted alternating diarrhea and constipation, 6 patients complained of constipation alone, and only 3 complained of diarrhea. One of the latter had had a previous abdominoperineal resection for carcinoma of the rectum and had numerous trophozoites of *ameba histolytica* in the stool. From the diversity of the pattern of alteration noted in these 17 patients, it would appear more advantageous to stress the occurrence of change rather than the development of inexplicable diarrhea in possible cases of carcinoma of the cecum.

Passage of blood from the large intestine was noted by 11 patients (33.33 per cent), 2 of whom had requested examination for this reason. The other 9 had been aware of bleeding over a period of time, but came for examination primarily because of other complaints. The bleeding was slight in 4 patients, moderate in 3, and severe in 4.

Three patients (9.09 per cent) were aware of the presence of a mass in the right lower abdominal quadrant at the time of the initial examination. Although this was the primary reason they decided to consult a physician, there were usually associated complaints of pain, loss of weight, weakness and, in one instance, persistent vomiting.

The lapse of time between development of these symptoms and definite diagnosis and treatment was most revealing. Admittedly, these symptoms are complications or secondary manifestations of carcinoma of the cecum; yet it was not unusual for patients to be aware of these symptoms for several months to one year or more prior to establishment of the true diagnosis. The incidental discovery of carcinoma, as in one of our patients at the time of laparotomy for another condition, has also been previously reported<sup>5</sup>. Usually, these patients had sought medical attention several months after the development of symptoms and had been relieved by medication. With return or increased severity of symptoms further examination was requested. It was not unusual to learn that a patient had been seen briefly by several physicians before being thoroughly

TABLE I  
BOWEL HABIT CHANGE

	No.	%
Constipation .....	6	18.18
Both (alternating) .....	6	18.18
Diarrhea .....	3	9.09
Bleeding .....	2	6.06
	17	51.51

examined. On the other hand, several patients had obviously delayed seeking medical attention in spite of pronounced symptoms over many months. Thus, the physician and the patient were equally responsible for the delay in diagnosis. The final factor in furthering diagnosis seemed to be the pronounced aggravation of symptoms already present or sudden change in the type of symptoms.

#### PHYSICAL CHARACTERISTICS

Several striking physical characteristics were noted among this group of patients. *Anemia*, so frequently cited as accompanying the development of carcinoma of the cecum, was prominent. Some patients were aware of pallor, but this was recorded as notable in 16 of the 33 patients. This was substantiated and made more striking by laboratory determinations of the hemoglobin and hematocrit. Twenty-one (63.63 per cent) of the 33 patients had less than 12 gm. of hemoglobin per 100 c.c. and 23 (69.69 per cent) had an abnormally low hematocrit.

In 22 patients, *abdominal tenderness* was noted on examination. As might be anticipated, this varied widely in degree and location, frequently being accompanied by rigidity of the abdominal muscles. Eight patients had definite symptoms and physical signs of lower small intestinal obstruction.

A mass in the right lower abdominal quadrant was found on examination in 24 patients (72.72 per cent). As many were mobile as were fixed. Although this high incidence is not unusual among such cases, the presence of a mass represents a late stage of the disease.

#### ROENTGENOGRAPHY

Whereas a positive diagnosis of carcinoma of the cecum was made in 24 of 32 cases (75 per cent) following roentgenographic examination, in only one instance was a flat plate of the abdomen or examination by barium enema not contributory in establishing the presence of some abnormality in the region of the cecum. In several instances, following demonstration of dilated loops of ileum and irritability of the cecum, or inability to fill the cecum at fluoroscopy, the presence of a lesion was inferred, and another examination requested.

TABLE II  
EXTENT OF TUMOR AT OPERATION

Limited to cecum .....	14
Contiguous Invasion .....	14
Invasion and metastasis .....	4
	32

The etiology of carcinoma of the cecum is not within the scope of this survey, but the roentgenographic reports add emphasis to the clinical impression that by far the greater number of these lesions arise in preexisting polyps. A polypoid lesion of the cecum was reported in 9 patients following examination by barium enema. Often, additional small polyps were found in the cecum and ascending colon in these patients on examination of the specimen following resection. One patient had undergone abdominoperineal resection for polypoid carcinoma of the rectum 11 years prior to resection of the right colon for polypoid carcinoma of the cecum. In addition, 2 other patients were found to have early carcinoma of the colon, on subsequent examination. One of these appeared in a polypoid lesion of the descending colon, and the second had a carcinoma of the rectum operated upon elsewhere.

#### SURGICAL TREATMENT

Operation was performed on 32 of the 33 patients. The remaining patient was admitted to the hospital *in extremis* from intestinal obstruction. In the course

of preoperative preparation a large mass was palpated in the right lower abdominal quadrant. The liver margin was firm, irregular and slightly tender. The patient died shortly after admission and carcinoma of the cecum with widespread metastasis was proved at autopsy.

Among the remaining cases, the observations at operation are of interest (Table II). The process was believed by the surgeon to be limited to the cecum in 14 patients. In an equal number invasion of contiguous structures or metastasis to the regional lymph nodes had occurred. In the remaining 4 patients, the carcinoma involved contiguous structures, and regional lymph nodes, and other metastatic foci were noted.

In spite of the gloomy outlook reflected by these operative observations, in many instances carcinoma of the cecum can be resected with removal of the regional lymph nodes and excision of contiguous tissue. In the present series the lesion was resected in 25 cases (75.75 per cent). Excision of the lesion entails removal of the right colon with a portion of the terminal ileum and performance of ileotransverse colostomy. This was done at one stage in all but one case, in

TABLE III

	No.	%
Resection .....	25	75.75
Short circuit .....	5	15.15
Exploration only .....	2	6.06
Unoperated .....	1	3.33

which the anastomosis was performed as a second stage. A short circuit ileotransverse colostomy was performed in 5 patients because of complicating intestinal obstruction in an otherwise inoperable situation. Resection was not done because of widespread abdominal metastasis in 2 patients, who showed no evidence of obstruction at the time of exploration (Table III).

#### PATHOLOGIC CLASSIFICATION

All except one lesion were graded pathologically according to the Dukes classification. As shown in Table IV, there was no instance of Dukes A lesions among these patients. Although the surgeon considered the lesion to be confined to the cecum in 14 cases, 6 of these revealed microscopic evidence of involvement of the serosa and regional lymph nodes.

#### MORTALITY

Four of the 32 patients operated upon died in the hospital, a hospital mortality rate of 12.5 per cent. One patient died from cardiac insufficiency on the first postoperative day. This patient had been admitted to the hospital following

the insidious onset of complete obstruction of the lower small intestine one week previously. He had been confined to bed because of weakness and abdominal pain for several months. An ileotransverse colostomy was done for obstructing carcinoma of the cecum. The second death occurred in a diabetic man admitted with abdominal pain, loss of 50 lbs. in weight, severe secondary anemia, and a palpable mass in the right lower abdominal quadrant. Following preparation right colectomy with ileotransverse colostomy was performed. On the sixth postoperative day a phlegmon of the abdominal wall developed and spread rapidly. The patient died on the 14th postoperative day; the phlegmon, despite debridement and intensive therapy, involved the tissues extending from the right axilla to the right groin and scrotum and left flank. The third patient died on the 15th day following exploration and biopsy as the result of congestive heart failure and terminal uremia. The fourth death resulted from a pulmonary embolus on the eighth postoperative day in a patient who had had an otherwise

TABLE IV  
PATHOLOGICAL GRADING (DUKES)

Dukes A .....	0
Dukes B .....	8
Dukes C .....	18
Dukes D .....	6
Not graded .....	1
	33

uneventful recovery following ileotransverse colostomy for nonresectable carcinoma of the cecum.

#### RESULTS

Of the 28 patients operated upon, 27 have reported for subsequent examination. It has been impossible to locate the other patient.

Of the two patients on whom exploration and biopsy was carried out, one died in the hospital and the other survived for one year. This patient had received several courses of nitrogen mustard therapy as a palliative measure.

Only one of the five patients on whom palliative ileotransverse colostomy was performed survived a comparable period. A second died seven months and a third three months postoperatively. The remaining two died shortly after operation, as mentioned previously.

In 25 patients resection of the right colon and terminal ileum with ileotransverse colostomy was performed. One of these died shortly after operation and it has been impossible to trace another. Of the remaining 23 patients, seven

died of recurrent metastasis within 14 months following operation. The remaining 16 (48.48 per cent) are well or without evidence of metastasis for varying periods.

These results are much more significant when correlated with the Dukes' classification of the individual cases. Of eight patients with Dukes B lesions seven survived. Of the 18 patients with Dukes C lesions, nine are alive. This emphasizes once again the excellent possibility of cure if carcinoma is diagnosed and treated early.

#### CONCLUSIONS

The results of this analysis of 33 proved instances of carcinoma of the cecum substantiate previous observations and focus attention on others that were apt to be regarded as unimportant. From this group of cases it would appear that carcinoma of the cecum develops in males at an earlier age than in females. The large number of patients reporting for examination with a long history of abdominal pain and secondary evidence of loss of weight and anemia underscores the necessity of complete examinations, repeated if need be, in individuals that are apt to be considered as psychoneurotic.

Perhaps the high incidence of notable change in bowel habits or bleeding from the intestine may lend further argument to the need for thorough investigation of the patient by the physician before he dismisses him with instructions to take multivitamin and iron preparations.

Once again, the great difference in prognosis following operation for early or fully resectable carcinoma and for advanced lesions is apparent. This recurrent plea for early diagnosis should include advocacy of abdominal exploration if there are definite indications of carcinoma without demonstrable roentgenographic evidence.

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## HYPERCHLORHYDRIA—CAN IT BE CONTROLLED MEDICALLY?\*

EDWIN BOROS, M.D., F.A.C.G.

New York, N. Y.

Hyperacidity of the gastric juice is a frequent and significant disorder, and though its presence as such in the normal state is not unusual, much attention has been focused on this item both for study as well as for control with varying measures of success and progress. At the present time, there is no satisfying knowledge as to its complex mode of origin or behavior. Constant changes in the volume of the gastric secretion contributes much to the difficulties in evaluating altering chemical changes which are being occasioned by local functional disturbances or reflex action from distant sources.

That hyperchlorhydria is a finding of considerable clinical significance is unquestioned. The extent of its occurrence in persons without symptoms cannot be measured. Patients subject to its existence may manifest either mild, transient or severe complaints of a formidable character embracing the fields of gastritis, peptic ulcer, carcinoma, nervous reflex, hormonal or possible chemical causes. That it plays an important role in the production of peptic ulcer has been acknowledged by both the clinician and surgeon<sup>1</sup>. But it is by no means certain that it causes it. Porges<sup>2</sup> maintains that where there is no acid there is no ulcer. Mann and Williamson<sup>3</sup> showed that both acid and pepsin secretion of the gastric juice contributes to the chronicity of duodenal ulcer. Other factors such as tissue resistance, local vascular changes or hormonal effects may play a vital part in the etiology of ulcer. The rationale of vagotomy is based on the belief that the primary disturbance in an ulcer state resides not in his stomach but in his brain. Furthermore, support in favor of this type of surgical approach lies in the experience that when vagotomy is complete nonrecurrence of the lesion is the rule<sup>4</sup>. A reduction of the gastric secretion may likewise be effected by the pharmacologic blocking of the vagus impulses with the use of parasympatholytic drugs. An intense increase in the digestive power of acid takes place in the presence of pepsin. A pH of 3.5 or higher is generally regarded as being necessary to abolish nearly all peptic digestion, this figure being the upper level at which Toepfer's Reagent indicates the presence of free acid. Schoch's studies<sup>5</sup> concluded that the inhibition of pepsin is consequent to the alteration of the pH, and that its activity decreases as the pH value increases towards neutrality.

Hyperacidity not infrequently resists medical control<sup>6</sup>. At times surgery is required. To what degree does this persistence depend on the failure of adequate binding of the free acid of the gastric juice? Could it be that incomplete neutralization lies at the root of the refractory ulcer?

\*Read by title before the First Annual Convention of the American College of Gastroenterology, Washington, D. C., 25, 26, 27 October 1954.

This study is pursued for the purpose of ascertaining the degree of neutralization possible by the administration of food and alkali and to establish if such a state can be accomplished. It must be emphasized that a reduction in acid as distinguished from complete neutralization is by no means a mere refinement and can only be regarded in its true aspect. A real concept of therapy can only be predicated upon accurate knowledge as to what actually can be accomplished when an attempt at control of hyperchlorhydria is effected. Friedenwald<sup>7</sup> in 1937 decried the lack of evidence available with regard to the degree of neutralization actually obtained by the use of gastric antacids. Three years later, Kirsner<sup>8</sup>, while investigating the effects of various antacids on the hydrogen ion concentration of gastric juice, sought to determine just what could be considered actual neutralization. He found this question difficult to answer. It has been assumed generally, that the mere administration of alkali results in a complete combination of the free hydrochloric acid. Yet, despite energetic and sustained efforts at acid control, a massive hemorrhage or perforation of an ulcer has been found to be a not unusual experience in the course of actual treatment which includes not only dietary measures but recourse to parasympatholytic drugs as well. The occurrence of such phenomena in the face of a therapeutic approach which could anticipate otherwise, invites a reappraisal of accepted thought and procedure, and while it is not presumed that the entire phase of hyperacidity or ulcer could be unravelled in this study, an attempt at clarifying the acid reaction to alkali in the gastric contents seems not only justifiable but necessary. It may be but one facet in an intricate and complicated mechanism.

Accordingly, a series of patients with digestive complaints accompanied by hyperchlorhydria were selected for study. The plan was as follows. A fasting gastric contents is obtained on the morning of examination. Immediately thereafter, four ounces of milk is drunk. The patient is intubated in one-half hour and calcium carbonate, one teaspoonful, is given with a small amount of water. One-half hour later, the contents are again withdrawn. This routine is carried out over a full three hour period, making a total of seven specimens of gastric extracta. A day or so later, the same patients, where possible, were again intubated. After the withdrawal of the fasting secretion, a meat sandwich with some water was consumed by the patient. Thereafter, at one-half hour intervals, calcium carbonate in one teaspoonful doses was administered as previously, prior to which withdrawal of the ingesta had been effected at each occasion. A feature of the method of examination which merits mention is the recourse to the use of a Levin tube which is introduced through the nostril (when possible), and immediately withdrawn after suction of the sought for secretion had been accomplished. This consumes no more than five or six seconds, ease and speed of manipulation being emphasized. None of the patients examined were subjected in this way to any noticeable unpleasantness or revulsion on their part, and from the standpoint of possible mechanical factors which an

indwelling tube is more likely to occasion, this method was thought to portend a lessened likelihood of psychic or mechanical trauma which might distort the results. It is assumed more or less universally that a retained gastric tube does not act as a foreign body, nor by its position *in situ*, initiate salivary, esophageal

TABLE I  
PEPTIC ULCER PATIENTS

Fasting Contents	% hour after milk	1 hour after calc. carb.	1½ hours after milk	2 hours after calc. carb.	2½ hours after milk	3 hours after calc. carb.
M. 35-60	25-48	25-45	25-50	5-50	15-65	0-45
R. 25-50	50-85	2-52	10-70	0-55	2-67	0-44
R. 5-30	20-50	10-60	6-48	0-36	4-40	0-32
R. 10-20	40-45	0-20	0-30	20-30	20-40	0-10
K. 60-75	50-70	10-50	25-50	0-50	15-55	0-45
K. 50-60	40-60	20-40	20-50	15-45	0-40	0-40
F. 40-55	15-75	0-40	10-70	0-50	15-65	0-50
H. 50-80	30-85	0-5	0-5	0-4	0-50	20-40
F. 15-45	30-65	0-40	10-60	10-45	10-50	5-50
W. 30-36	40-100	0-20	0-18	0-10	0-30	0-20
B. 20-40	30-70	10-40	0-60	0-30	0-30	0-30
C. 50-60	5-40	0-20	0-42	0-34	0-60	0-40
B. 30-40	30-80	15-60	30-60	0-40	20-50	0-60
C. 35-45	0-40	0-20	0-40	0-20	0-60	0-60
H. 30-50	40-85	0-10	40-90	0-10	0-40	0-28
F. 0-25	0-17	0-15	8-10	0-20	0-25	0-20
M. 30-50	20-80	0-16	4-24	0-10	0-18	0-24
S. 60-80	55-77	0-45	5-55	0-40	7-50	2-27
S. 12-44	4-40	0-35	20-60	0-30	12-35	0-30
L. 25-50	8-43	3-33	15-55	0-40	10-65	0-45

The figures represent clinical units (number c.c. N/10 NaOH required to neutralize 100 c.c. gastric juice)

1st figure—free HCl.

2nd figure—total acidity

or gastric irritation or stimulation, not to speak of the disturbed psychic features which might be brought into play in the process. Convincing evidence that this is so is by no means conclusive.

In using calcium carbonate to control gastric acidity one is reasonably assured that when administered in moderate doses no significant alteration of the acid base equilibrium takes place<sup>9</sup>. Its neutralizing effect has been attested to by several investigators<sup>10</sup>. Incidentally, such action depends not only on chemical factors but also upon the continued rate of secretion of the hydrochloric acid and the state of gastric motility. Rapid gastric emptying furthers a high acid curve. Dilution is less apt to occur under these circumstances<sup>11</sup>. Kirsner<sup>6</sup> in a study of 25 cases confirmed the effective neutralizing value of

TABLE II  
PEPTIC ULCER PATIENTS

Fasting Contents	% hour after meat	1 hour after calc. carb.	1½ hours after calc. carb.	2 hours after calc. carb.	2½ hours after calc. carb.	3 hours after calc. carb.
F. 60-72	52-82	15-65	22-72	4-44	7-37	15-45
R. 40-50	20-30	0-12	0-10	0-5	0-5	0-5
K. 60-70	40-100	0-40	30-50	30-50	40-60	0-40
F. 20-40	10-80	0-30	10-40	0-40	5-25	0-25
H. 40-50	30-60	0-60	40-70	0-60	15-40	0-20
W. 30-50	20-40	0-15	60-90	55-90	55-70	0-10
S. 2-42	0-55	0-40	0-55	0-40	5-38	0-35
C. 50-70	40-80	0-24	0-40	0-40	0-30	5-20
B. 10-45	35-105	5-35	20-70	0-50	8-64	0-62
C. 30-55	10-46	0-18	10-40	0-22	5-30	0-30
H. 40-60	50-80	0-20	10-70	0-20	0-30	0-20
F. 15-25	20-35	0-10	0-10	0-10	0-10	0-10
M. 60-80	30-55	0-30	26-41	10-26	5-20	0-20
S. 27-54	40-70	12-32	20-40	2-42	35-67	0-35
S. 18-48	50-70	5-35	60-80	2-37	0-45	0-30
K. 35-45	40-80	25-80	27-92	0-50	5-52	0-57

calcium carbonate in two to four gram hourly doses and regards it as most superior. Warren<sup>12</sup> presented evidence that this compound possesses a definite pepsin-inhibiting effect when administered in the human being. It is noteworthy that frequent feedings alone have been known to reduce acidity. On the other hand, hyperchlorhydria is not always so easily controlled as shown by Machella<sup>13</sup> who reported the performance of a total gastrectomy to achieve a complete and permanent anacidity and effect a cure where there had been two vagotomies and a partial antral resection previously.

## COMMENT

Twenty duodenal ulcer patients were subjected to gastric analysis and chemical assay. The fasting contents in most of these patients were elevated above normal standards. In but three of this group was there a total and complete neutralization of free acid in all of the specimens extracted. The remainder showed varying degrees of hydrochloric acid in one or all of the specimens.

TABLE III  
HYPERACID NONULCER PATIENTS

Fasting Contents	% hour after milk	1 hour after calc. carb.	1½ hours after milk	2 hours after calc. carb.	2½ hours after milk	3 hours after calc. carb.
T. 40-50	30-45	0-10	15-45	0-10	0-10	0-40
B. 25-40	17-82	8-33	10-60	0-35	4-44	0-30
C. 30-40	15-65	3-33	0-55	0-30	0-55	0-25
carcinoma T. 35-45	40-60	30-40	30-50	40-60	15-20	38-48
S. 25-50	0-30	0-40	0-30	0-30	0-20	0-26
S. 5-30	12-62	0-44	2-54	0-32	0-47	0-27
P. 30-40	38-78	0-48	0-58	0-40	0-60	0-40
M. 50-60	20-100	0-25	15-55	0-60	0-55	0-20
M. 5-45	13-63	0-40	5-64	0-45	0-44	0-40
K. 25-50	25-55	0-44	0-46	0-40	0-30	0-36
G. 10-30	0-30	0-20	0-35	0-30	0-30	0-30
G. 20-40	0-56	0-20	0-40	0-35	0-45	0-40
F. 35-50	22-52	0-36	3-43	0-40	0-48	0-40
D. 10-30	0-20	0-20	0-30	0-30	0-25	0-40
B. 0-10	30-55	10-20	0-40	0-40	0-40	0-65
B. 20-42	32-72	0-40	0-65	0-40	0-50	0-40
A. 45-70	30-60	0-30	0-30	0-30	0-30	0-20
S. 5-30	25-45	0-35	15-65	0-30	0-25	0-25
K. 25-50	10-75	0-50	4-62	0-35	0-54	0-40
B. 70-80	0-20	10-20	10-30	0-25	0-42	0-20

The same procedure with the exception of the ingestion of meat rather than milk, appeared to parallel the findings of the previous group. In only one of the 16 patients studied in this way, was there evidence of a completely bound acid for the three hour period of observation. Moreover, the meat did not yield a high acid titer as expected, there being but a slight elevation in an occasional

case. Tables I and II show a disappointment in attainment of a consistent and persistent antacid response to the routine employed for its accomplishment. It will be noted that in the three hour extractions most of the figures finally reveal the neutralization level sought for.

Twenty-one patients with evidence of gastritis or functional disorders were made the subject of study. None of these had any history or signs of peptic ulcer. One of their number suffered from an operatively proved carcinoma of the stomach. The response in this series as presented in Tables III and IV were quite unlike those in the ulcer patients. Reduction of the free acid in the milk and

TABLE IV  
HYPERACID NONULCER PATIENTS

Fasting Contents	% hour after meat	1 hour after calc. carb.	1½ hours after calc. carb.	2 hours after calc. carb.	2½ hours after calc. carb.	3 hours after calc. carb.
T. 0-20	40-45	0-24	30-50	0-30	30-40	30-34
B. 32-45	35-70	10-45	10-55	0-45	2-47	0-35
C. 0-30	25-50	5-45	8-35	0-40	5-35	0-32
T. 15-45	40-60	20-40	46-66	0-34	0-20	0-20
M. 0-30	0-50	20-50	30-60	0-40	0-30	0-30
K. 32-70	10-30	4-24	4-40	0-30	0-36	0-32
G. 0-25	0-40	0-30	0-40	0-40	0-40	0-30
G. 20-50	0-40	0-20	0-40	0-14	0-40	0-20
D. 15-50	0-25	0-15	0-8	0-10	0-5	0-10
A. 25-45	20-40	0-40	0-50	0-40	0-40	0-20
L. 35-60	22-97	5-35	7-52	0-60	0-65	0-37
K. 32-52	28-94	12-36	20-40	0-30	0-60	0-31
B. 35-50	40-60	40-50	30-50	0-30	10-40	0-40

alkali group was much more satisfactory, with the exception of the carcinoma case, which resisted the effect of alkali completely. Those patients who were tested after the ingestion of meat behaved similarly. A common finding in the entire survey was the uniform pattern of practically uninfluenced acidity in all of the specimens obtained at the one-half hour period. It appears that the free acid does not yield immediately to measures directed towards its control.

While complete anacidity is not a requirement of ulcer healing, efforts are usually directed towards the attainment of such an end. Encouragement follows the usual comfort which is immediately apparent after the intake of alkali or food especially in an ulcer state. Nor can one overlook the rebound of acid

concentration just as soon as either is withdrawn. Furthermore, healing of an ulcer does not result in a permanent reduction of the original hyperchlorhydria. One wonders whether the emphasis which hydrochloric acid receives in the province of gastric disease is not erroneously projected into the forefront of cause when in reality it may be an effect. The acid values in the above tables after attempts at reduction, seem to dispel confidence that therapy can desirably control it. Moreover, considerable doubt is cast on the importance of achieving such an end. Clinical observation of the ulcer patients in the above series resulted in uniform improvement in the condition of each of them, employing practically the same therapy as was used in these experiments. None had any complications nor required surgery.

Hyperacidity in the nonulcer cases appeared to yield more rapidly to antacids. Aside from the suggestion that such response envisages possibly a more favorable or easier therapeutic result, a comparison of the more stubborn persistence to high values in the ulcer group in contrast to the nonulcer group with its much easier controlled acid suggests possible diagnostic considerations. The employment of the method described above may give diagnostic help in distinguishing the more benign forms of hyperchlorhydria from the peptic ulcer type. Whether the therapeutic response may be gauged from the acid readings after a three hour study will require further observation. Certainly, with the use of the routine as described, the behavior of the stomach can be better assessed than by the previous solitary Ewald analysis or Rehfuss method.

#### CONCLUSION

Attempts at complete neutralization of the hydrochloric acid in patients with hyperchlorhydria have been generally unsatisfactory. Calcium carbonate and food were used for this purpose. The duration of an acidity, when attained, is unpredictable as it is variable, although it was possible in some cases to effect complete neutralization. Hyperacidity on a nonulcer basis was more readily controlled. As an informative test of gastric secretory response, the routine use of alternating milk and calcium carbonate as described offers better prospects as a diagnostic aid and possible therapeutic guide than the solitary Ewald meal extraction or the Rehfuss method of gastric study. The star role which hydrochloric acid has assumed in the etiology and mechanism of gastric disease requires further clarification. Its position rather may well be one which is incidental to or the result of a disturbed local or distant process.

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## NEWER CLINICAL AND LABORATORY STUDIES IN THE AGED\*

### VII—TUBELESS GASTRIC ACIDITY DETERMINATIONS IN NORMAL GERIATRIC SUBJECTS

A. ALLEN GOLDBLOOM, M.D., F.A.C.G.

EDMUND G. HADRA, M.D.

JULIUS POMERANZE, M.D.

and

JOSEPH RECHTSCHAFFEN, M.D.

New York, N. Y.

With the greater number of population attaining and living a healthy life beyond the age of 60 and 70, and with a larger number of geriatric patients in our practice, it becomes essential for the profession to be cognizant of what "normal" metabolic geriatric functions may be. My associates and myself, were given the opportunity to study "normal geriatric medicine" within the past three years. This work emanates from the Bird S. Coler Memorial Hospital, in New

TABLE I

PRESENCE AND ABSENCE OF ACIDITY BY THE TUBELESS METHOD  
IN "NORMAL" GERIATRIC SUBJECTS

Tubeless Method for Acidity	Total Number Patients	Percentage
positive	66	69.5
negative	29	30.5

York City, an institution for chronic disease individuals, with a population of 1,900 patients. Known malignant and tuberculous conditions are not admitted to this hospital.

Our publications on serum lipid partitions and lipoprotein molecules<sup>1,2,3</sup> in normal geriatric subjects revealed low levels not related to malnutrition, avita-

\*Read before the First Annual Convention of the American College of Gastroenterology, Washington, D. C., 25, 26, 27 October 1954.

From the Medical Service of the New York Medical College, Metropolitan Medical Center (Bird S. Coler Hospital Division).

Aided by a grant from the Sophie D. Cohen and W. W. Cohen Foundation.

The quininium resin used in this study was generously supplied by the Squibb Institute for Medical Research, New York, N. Y. It is now manufactured under the trade name of "Diagnex".

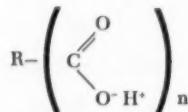
minosis, or wasting disease. Some authors mention the increasing frequency of permanent achlorhydria associated with age, anemia, progressive gastritis, debilitation, and malnutrition<sup>4</sup>. Since such conditions were excluded in our observations, we attempted to ascertain what percentage of "normal" geriatric subjects would show anacidity and the causes thereof.

The passing of a stomach tube presented special problems in these non-cooperative, suspicious, restless geriatric patients. Recent favorable reports of tubeless gastric analysis<sup>5-10</sup> prompted us to take the opportunity to determine the presence or absence of gastric acidity, in 95 normal male and female subjects 80-100 years of age.

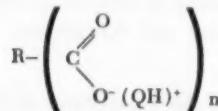
#### PRINCIPLE OF ION EXCHANGE RESINS

Cation exchange resins owe their reactivity to various functional groups one of which is the carboxylic grouping (COOH). Cation exchange indicator compounds may be prepared by replacing the hydrogen cations of the carboxylic acid groups present in cation-ion exchange resins with cations which are not normally present in the body. These can be replaced by hydrogen cations to determine the presence of free hydrochloric acid. Such conditions, called special indicator ions, must be nontoxic, readily absorbed from the stomach or small intestine, and easily detectable in the blood, urine, and/or saliva. Cation-ion exchangers such as Amberlite-IRC-50 or Amberlite XE-96, when subjected to the action of special indicator cations in aqueous solution, form a cation exchange ion indicator.

By the employment of this principle a quininium exchange indicator compound (Diagnex) has been produced, by Segal and his associates<sup>5,6</sup>.

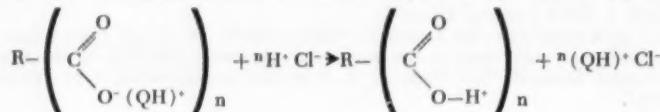


Amberlite (cation exchanger)



Diagnex (Quininium cation exchange indicator compounds IEC-QH)

When diagnex is subjected to the action of hydrogen cations of gastric hydrochloric acid the quininium cations are replaced by the hydrogen ions:



This compound contains approximately 18 mg. of available quinine per gram of resin. Doses of 2 grams are administered. The quinine hydrochloride so formed is absorbed from the small intestine and about  $\frac{1}{2}$  of it is then excreted in the urine. The first two hours after the oral administration of this indicator compound are the critical hours in the excretion of the quininium cations to determine whether the quinine cations have been displaced by the hydrogen ions of free gastric hydrochloric acid or to a lesser extent by the cations present in the secretions in the small intestines.

#### METHOD OF STUDY

All medications such as steroid compounds, vitamin preparations, quinine or related drugs and sedatives were omitted on the day preceding the test. No

TABLE II

DIFFERENCE BETWEEN TUBELESS AND INTUBATION METHODS FOR  
ACIDITY DETERMINATIONS IN "NORMAL" GERIATRIC SUBJECTS

Tubeless Method	Intubation Method		Percentage
Negative	Negative	Positive	
24	24	—	88.9
3	—	3	11.1
Total	27	24	100.0
Refused	2		

food was permitted after midnight. On arising, the patient was instructed to urinate and discard the specimen. Breakfast and liquids were omitted. A capsule containing 250 mg. of caffeine sodium benzoate was given, followed by a glass of water, coffee, or tea without cream, milk or sugar. Secretory stimulants such as histamine diphosphate were not used because of the advanced age of the patients. One hour later the patient voided and the entire quantity of urine collected marked as "control urine". A mixture of 2.0 gm. of quininium resin was emptied into a glass of water, stirred well, and given to the patient. Urine was collected one hour and two hours after taking the resin compound. The specimens were marked "2" and "3". The patient was told to empty the bladder completely each time. If urination ahead of a scheduled time was necessary the

amount was added to that passed at the next designated time. In the last 25 subjects this procedure was modified in that only a single test specimen of urine was collected two hours after the administration of the resin compound. No urine was collected after the 2 hour period.

#### TECHNIC OF ANALYSIS

A control sample of urine and specimens voided one and two hours after the administration of the resin compound were collected and examined for

TABLE III

GASTROINTESTINAL CONDITIONS ENCOUNTERED IN "NORMAL" GERIATRIC SUBJECTS  
BY X-RAY SERIES WITH THE PESENCE OR ABSCENCE OF GASTRIC ACIDITY  
BY THE URINARY METHOD

X-ray Diagnosis	Patients X-rayed		Tubeless Method for Acidity Determination		Negative Urinary Acidity Tests Compared to Intubation Method	
	Number	Per cent	Positive	Negative	Positive	Negative
Normal	23	52.3	14	9	1	8
Pylorospasm	5	11.3	5	—	—	—
Hiatus hernia	4	9.0	3	1	—	1
Prolapse gastric mucosae	4	9.0	2	2	—	2
Duodenal diverticulum	2	4.4	1	1	—	1
Gastric ulcer	2	4.4	2	—	—	—
Antral gastritis	1	2.4	1	—	—	—
Cancer of stomach	1	2.4	1	—	—	—
Duodenal ulcer	1	2.4	1	—	—	—
Duodenitis	1	2.4	1	—	—	—
Total	44	100.0	31	13	1	12

quinine content by measure of their fluorescent intensity against standard solutions under ultraviolet lights. The ether-sulfuric acid technic described by Kelsey and Geiling<sup>11</sup> and as employed by Segal and his associates was utilized<sup>5,6</sup>. The procedure and method of preparing standard solutions were described in detail in a previous publication<sup>12</sup>.

#### INTERPRETATION OF FLUORESCENCE

The control sample of urine must first be determined for fluorescence. If the result shows fluorescence corresponding to 15 mcgm. or more of quinine,

the test is disregarded and repeated after a week. This may be evidence that the medications as B-complex vitamins, quinine, or steroid compounds were not eliminated. If the result on the urine control corresponds to 5 to 15 mcgm. of quinine the urine samples may be examined. The amount of fluorescence seen in the control must be subtracted from each of the two test samples. If the amount of fluorescence of the urine control corresponds to less than 5 mcgm. of quinine, it can be ignored and not subtracted. The total of the 2 specimens of urine or the second hour specimen should result in 25 mcgm. of quinine or more to determine the presence of free gastric hydrochloric acid. A range of 15 to 25 mcgm. of quinine may be evidence of hypoacidity. The test is repeated after seven days or corroborated by intubation.

TABLE IV

COMPARATIVE PERCENTAGE VALUES OF TUBELESS METHOD FOR ACIDITY DETERMINATIONS IN "NORMAL" GERIATRIC SUBJECTS WITH NORMAL AND VARIED INSIGNIFICANT X-RAY FINDINGS

Status	Number of Individuals	Urinary test for gastric secretion of hydrochloric acid—percentage	
		Positive	Negative
Total	95	69.5	30.5
Normal G.I. X-rays	23	60.9	39.1
Varied G.I. X-ray findings	44	70.4	29.6

#### RESULTS OF STUDY

Ninety-five male and female "normal" subjects, age 80 to 100 years were studied. The conditions commonly encountered were arthritis, hemiplegia, multiple sclerosis, Parkinsonism, diabetes, etc. Many patients were here because of social and economic domestic conditions.

Of the total of 95 normal geriatric subjects studied 66 (69.5 per cent) had acidity while 29 (30.5 per cent) had no acid (Table I). The 29 individuals who exhibited achlorhydria with the tubeless method were checked by gastric intubation. Twenty-seven such determinations were made. Three negative urine tests revealed three positive results for acidity with the tube method, showing a discrepancy of 11.1 per cent and a comparative value of acidity both by gastric analysis and urinary examinations of 88.9 per cent (Table II).

Forty-four subjects had gastrointestinal x-ray examinations (Table III). Twenty-three individuals had a negative x-ray finding (52.3 per cent). Fourteen

of these 23 subjects demonstrated the presence of acid by the urinary test (60.9 per cent). The other x-ray diagnoses were of no significance except for one case of antral gastritis with hyperchromic macrocytic anemia, one with gastric malignancy, one with duodenal ulcer and two with gastric ulcer. Interestingly the above individuals displayed acidity by the tubeless method.

The comparative value of the positive tubeless method for acidity determination (69.5 per cent) in all 95 subjects approximated that encountered with negative and varied insignificant gastrointestinal x-ray findings (70.4 per cent) in 44 individuals (Table IV).

#### DISCUSSION

Achlorhydria is uncommon in healthy infants and children and its occurrence is noted more frequently with advancing age<sup>13</sup>. Vanzant and associates found 14.5 per cent of apparent achlorhydria<sup>14</sup> in patients with no diseases of the gastrointestinal tract. The incidence of achlorhydria dropped slightly after the age of 60 suggesting that persons with achlorhydria are not so hardy or so long-lived as those who have strongly acid gastric juice. Achlorhydria is slightly more common in the female than in the male according to some observers<sup>15</sup>. Winkelstein<sup>16</sup> found the percentage of achlorhydrias among 5,585 patients was 2.2 per cent. Pollard<sup>17</sup>, using the histamine test, found 10.4 per cent of achlorhydria in males and 14.1 per cent in females. Faber<sup>18</sup> explains the increasing frequency of permanent achlorhydria with age by the progression of gastritis. Rafsky and Weingarten<sup>19</sup> found 17.0 per cent of achlorhydria in normal patients past 65 years of age, none of whom had peptic ulcer syndrome. Our studies show a greater frequency of achlorhydria (30 per cent in normal geriatric subjects) than the above observers. Debilitation, marked anemia, malnutrition and progressive gastritis were not present in our geriatric subjects.

#### CONCLUSIONS

1. Tubeless gastric acidity was studied in "normal" geriatric subjects 80-100 years of age, male and female.
2. Achlorhydria was found in 30 per cent of "normal" geriatric subjects while acidity was present in 70 per cent of the individuals, aged 80-100 years.
3. Gastrointestinal x-rays showed normal studies in 52 per cent of the subjects. Only one case of gastric malignancy, two of gastric ulcer and one of duodenal ulcer were encountered.
4. Positive tubeless gastric acidity values (69.5 per cent) approximated the normal and insignificant gastrointestinal x-ray findings (70.4 per cent).
5. Discrepancy between the negative tubeless gastric acidity method and the positive intubation for acidity was 11.1 per cent.

6. The convenience and economy of the tubeless gastric acidity method makes it possible to screen large numbers of patients and eliminate unnecessary x-ray examination.
7. The urinary test for gastric secretion of hydrochloric acid (tubeless method) should be advocated in geriatric patients and in conditions that would contraindicate intubation.

#### ADDENDUM

Since the above manuscript had been submitted, the senior author examined other patients with a newer preparation called "Diagnex Improved". This is a carboxylic resin indicator with azore A replacing quinine as the indicator cation for the detection of anacidity without intubation<sup>20</sup>. This determination is very simple and can be carried out in the physician's office without any special apparatus or technical help.

The results are practically 100 per cent as compared to the intubation method<sup>21</sup> and confirms that already reported by Segal and his associates<sup>20</sup>.

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## MASSIVE HEMORRHAGE DUE TO DIVERTICULA OF THE COLON

ARNOLD STANTON, M.D.

Richmond Hill, N. Y.

Diverticular disease of the colon is becoming a more common condition due to improved diagnostic methods, chiefly the widespread use of x-ray examinations of the intestinal tract. Another factor is the increase in longevity. The aged in our country continue to increase rapidly in number as well as in proportion to the total population.

Diverticula may be found anywhere in the gastrointestinal tract; only occasionally in the esophagus, stomach and small intestine, more frequently in the duodenum and commonly in the colon, especially in the sigmoid and descending colon. In about 35 per cent of cases they are confined to the sigmoid portion of the colon and in a further 40 per cent they are found scattered throughout the colon in addition to the sigmoid. They are usually acquired and are frequently multiple. Diverticula are blind sacs with narrow necks branching out from the bowel and vary in size from microscopic dimensions to 2-4 cm. in diameter. Although the etiology is incompletely understood, it is commonly believed that the herniations occur at the points of entry of blood vessels into the intestinal wall or defects in the muscle or fat. Increased intraluminal pressure plays an important role. The wall is composed of mucosa, submucosa and peritoneum but lacks a muscular coat. The narrow neck, the solid character of the feces and this lack of a muscular coat cause difficulty in the expulsion of fecal material from the sac and results first in irritation, then inflammation of the mucosa lining the wall of the sac. This leads to spasm of the bowel and causes the common symptoms of abdominal cramps and diarrhea. Intestinal tension is greatest in the descending colon and sigmoid and causes these areas to be most susceptible to stretching and thinning.

Carlson and Hoelzel<sup>1</sup>, from observations on rats fed various types of diets, indicate that sac formation may be due to herniation of the weakened part of the wall of the colon into a fat infiltrated peritoneal sacculation. They were able to bring about increased intracolonic pressure and produce diverticula by feeding the animals a concentrated low residue diet that caused continuous contraction. They concluded that bulky diets prevented the development of diverticula of the colon. Diverticula of the colon occur in 5-10 per cent of people over 45 years of age and diverticulitis takes place in 15 per cent of these. Diverticulitis may have protean manifestations and the diagnosis must be thought of in any patient past middle age with abdominal symptoms. An elderly patient with lower abdominal pain, especially left-sided, together with constipation or diarrhea should be suspected of having diverticulitis, although malignancy must be ruled out. Diverticulitis must also be considered in a patient in

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From the Department of Medicine of the Queens General Hospital, Jamaica, N. Y.

TABLE I  
MASSIVE HEMORRHAGE DUE TO DIVERTICULA OF THE COLON

Case No.	Date of Admission	Age Sex	Mode of Onset	Lowest Hb.(gm.)	Blood Count RBC	WBC	Associated Conditions	Blood Given	Hospital Days	Location by X-ray
1	10/16/52	69 F	Tarry stools Syncope	3.0	9,150		Arteriosclerosis of abdominal aorta	2,000 c.c.	30	Descending and sigmoid
2	10/ 6/50	70 M	Bloody stools for 3 days shock	7.0	2.5		Heart Disease	1,500 c.c.	5 hrs.	
3	12/ 2/51	64 M	Pool of blood on bathroom floor	11.5	10,300			500 c.c.	16	Sigmoid
4	5/28/50 Readmission 7/22/51	75 M 76	Large bloody stool; Syncope Rectal bleeding for 18 hours	11.5 11.5	7,400 21,300		Heart Disease Enlarged Heart	500 c.c. 500 c.c.	7 4	Transverse descending and sigmoid
	Readmission 11/ 5/51	76	Bloody stools	14.0	4.2	7,700			500 c.c.	21
5	9/ 4/50	83 M	Sudden bleeding from rectum; Semi-Stupor	6.9	1.87	14,300	Enlarged Heart	2,500 c.c.	28	Sigmoid

6	5/16/50	69	M	Bleeding for 3 days	5.5	1.85	12,200	Diet for weight reduction; Enlarged Heart	2,500 c.c.	18	Descending and sigmoid
7	11/28/50	81	F	Bloody stools for 2 days	5.0	2.4	12,800	Enlarged Heart & Hypertension & Stroke	2,000 c.c.	22	Descending
8	8/31/50	66	M	Sudden bleeding before admission—Shock	6.3		24,200	Hypertension & CVA Enlarged Heart	1,500 c.c.	41	Ascending
9	9/21/51	75	M	Rectal bleeding for 3 days	7.5		13,000	Left Ventricular Hypertrophy	1,500 c.c.	14	Descending and sigmoid
10	6/30/52	73	M	Bloody stools for 4 days	7.5	1.9	5,000	Hypertension Enlarged Heart	1,000 c.c.	6	Sigmoid
11	10/15/50	67	F	5 bloody movements & collapse	7.8	2.5	11,200	Enlarged Heart	500 c.c.	13	Transverse and descending
12	1/31/53	73	M	Passed large amount of blood			5,500		500 c.c.	12	Descending and sigmoid
13	12/13/52	71	F	Sudden rectal bleeding	12.5		9,200	Enlarged Heart Hypertension Congestive Failure	500 c.c.	14	Descending and sigmoid
14	8/28/50	81	M	10 bloody movements Shock	9.5	3.3	9,300		500 c.c.	18	Sigmoid

the older age group with symptoms and signs of peritonitis, abscess, intestinal obstruction, fistula formation or rectal hemorrhage. The bleeding may be occult, gross, or massive in character.

The incidence of bleeding is recorded as occurring in 4-30 per cent of reported cases of diverticulosis and diverticulitis of the colon. While Rankin and Brown<sup>2</sup> found melena in 39 of 142 cases, they concluded that the bleeding of only 19 or 13 per cent was actually due to diverticulitis. Ochsner and Bargen<sup>3</sup> found rectal bleeding in 6 per cent of their cases. They found that 5 per cent of cases of diverticulosis showed bleeding whereas 22 per cent of cases of diverticulitis complained of melena. Willard and Bockus<sup>4</sup> found 7 per cent of 72 cases in which gross rectal bleeding was due to diverticula, although occult bleeding occurred in 11 per cent. Bleeding occurred equally as often in diverticulitis as in diverticulosis. Brown and Marcley<sup>5</sup> found bleeding not attributable to other causes in but 4 per cent of their cases. H. B. Stone<sup>6</sup> in an interesting discussion of melena of obscure origin reported 8 cases of bleeding from the gastrointestinal tract for which diverticula of the colon were responsible. In 1944 Young and Young<sup>7</sup> found blood in the stools in 26 per cent of their series where no cause other than the diverticulitis was found. They noted that the incidence of bleeding was much higher in their series than was found in a review of the literature (5-17 per cent). J. J. Morton, Jr.<sup>8</sup> found bleeding present in 20 per cent of his cases, a much higher figure than expected. Le Royer and White<sup>9</sup> reported that melena occurred in 16.5 per cent of their cases and wrote that bleeding occurred in diverticulitis more often than was generally believed. G. C. Turnbull<sup>10</sup> found that of 151 patients with diverticular disease of the colon admitted to the hospital, 9 had massive rectal hemorrhage of whom 5 required transfusions. C. Rosser<sup>11</sup> reviewed the incidence of rectal bleeding in diverticulitis and found that bleeding existed in 30 per cent of his 40 cases.

Diverticulosis and diverticulitis of the colon are associated with massive rectal hemorrhage much more commonly than is generally appreciated.

The sudden passage of a large amount of blood from the rectum, accompanied by varying degrees of shock, is a dramatic and alarming occurrence that calls for emergency diagnostic and therapeutic measures. The picture is that of an older individual in previously good health who has been usually sedentary and perhaps constipated and who is suddenly seized with lower abdominal crampy pain and an urgent desire to move his bowels. There may be one or more loose movements of bright red, tarry or dark red blood. The patient complains of a feeling of faintness and upon examination is pale and weak, with a low blood pressure, rapid pulse and other indications of shock.

#### CASE REPORTS

*Case 1:*—A 69-year old female entered the hospital on October 16, 1952, because of extreme weakness of one year's duration and inability to walk for

the week preceding admission. For the past year she had been aware of increasing fatigue progressing to weakness which became so marked that during the week before admission she was unable to walk and had to crawl around her home. She was reduced to drinking liquids because she was too weak to swallow solid food. The patient fainted prior to admission and a physician was called who advised immediate hospitalization. She had lost weight during the past two years and had constipation alternating with bouts of diarrhea. Of late, her stools had been continuously black and tarry.

Physical examination disclosed a very weak, poorly nourished elderly female. Her skin was lemon yellow in color. She had no dyspnea and was comfortable in bed. Her blood pressure was 150/60 mm. Hg. The heart was not enlarged and there were no murmurs. The cardiac rhythm was regular and the rate 100 per minute. The liver was smooth and enlarged 3 fingers' breadth. The stools were black in color. The hemoglobin was 3 gm. The white blood count was 9,150. The urea nitrogen was 9 mg. per 100 c.c. The clinical impression was pernicious anemia or carcinoma of the gastrointestinal tract.

Sternal marrow examination showed the presence of secondary anemia but no pernicious anemia or other type of blood dyscrasia. She was given a transfusion of 500 c.c. of blood daily for the first 2 days. She ate very well but continued to pass tarry stools for the first week. At the end of this time she received her third 500 c.c. transfusion and her hemoglobin rose to 7.8 gm. Another transfusion of 500 c.c. of blood was given at the end of the second week, at which time her hemoglobin was 10 gm. Gastrointestinal series was negative. Gastric analysis showed the presence of free hydrochloric acid after stimulation with histamine. X-ray showed multiple diverticula throughout the descending colon and sigmoid, together with plaque-like calcifications of the abdominal aorta. She was discharged in good condition on her 30th hospital day after having received a total of 2,000 c.c. of blood.

*Comment:*—The profound anemia in this case bore a striking superficial resemblance to pernicious anemia. Extensive diverticulosis of the descending colon and sigmoid was the only finding to explain the source of the extreme blood loss.

*Case 2:*—A 70-year old male was hospitalized because of rectal bleeding on October 6, 1950. He had been well until he contracted a cold three days before admission and became constipated. He then took a laxative and had bloody stools since shortly thereafter. He vomited clear fluid once and developed pain in the lower abdomen. When seen by his physician, he was in a state of shock and was hospitalized. He had been told to take it easy because of heart disease.

Physical examination revealed a pale, elderly male covered with a cold sweat and gasping for air. His blood pressure was 80/60 mm. Hg., pulse 130 in

rate and weak in character, respirations 36 per minute and temperature 102.4°F. The heart sounds were barely audible. There were rales at both lung bases with expiratory wheezing rales. The liver was enlarged 2 fingers' breadth. The hemoglobin was 7 gm., red blood cell count 2,530,000 and hematocrit 21 mm. Rectal examination showed red blood on the examining finger. The clinical impression was lower gastrointestinal hemorrhage and shock, together with bibasilar pneumonia, arteriosclerotic heart disease and congestive heart failure. Within a few minutes of admission he received 250 c.c. of plasma followed by 500 c.c. of blood. The administration of oxygen was begun immediately. He was digitalized and given 300,000 units of penicillin every three hours. Following the initial blood transfusion, his blood pressure rose to 108/70 mm. Hg., but his pulse continued to be rapid and barely perceptible. He received two additional transfusions, but his blood pressure slowly dropped to 78/60 mm. Hg., his pulse remained rapid and weak and he expired 5 hours after admission.

At autopsy, the colon contained multiple diverticula and the contents of the colon were black and tarry. No hemorrhagic points could be identified. The stool in the remainder of the intestinal tract was light yellow in color. There was a fresh occlusion of the left anterior descending coronary artery  $1\frac{1}{2}$  cm. from the orifice, causing a myocardial infarction of two thirds of the anterior wall and involving the anterior three-quarters of the interventricular septum.

*Comment:*—Death was due to coronary occlusion with extensive myocardial infarction, apparently secondary to the blood loss of three days' duration due to the colonic diverticula. The chain of events started with a cold and constipation followed by the taking of a laxative and rectal hemorrhage.

*Case 5:*—An 83-year old male began to pass bright red blood from the rectum the evening of admission, September 4, 1950. He had been ailing the past two years with anorexia, weakness and weight loss. Diarrhea had started a few months prior to admission but he had been constipated the last week.

Physical examination revealed a semi-stuporous elderly male who was unable to give a history. His blood pressure was 150/80 mm. Hg. The heart was enlarged to the left and a soft systolic murmur was found at the apex. The abdomen showed a palpable ascending colon but no tenderness or rigidity. The hemoglobin was 8 gm. The red blood cell count was 2,900,000, white blood count 14,800, and hematocrit 28 mm. He was given 500 c.c. of blood upon admission followed by intravenous fluids. The next day his hemoglobin was 11 gm. and red blood cell count 3,300,000. The electrocardiogram showed a left heart strain pattern together with occasional nodal and ventricular premature contractions. The bleeding stopped for several days but hemorrhage recurred five days after admission and his blood pressure dropped to 130/70 mm. Hg. He was again given 500 c.c. of blood and an additional 500 c.c. of blood two days later because his condition remained poor. Ten days after admission he was found

in the morning lying in bed in a pool of blood and clots. His hemoglobin at this time was 6.9 gm., red blood cell count 1,870,000 and hematocrit 25 mm. He was immediately given 500 c.c. of blood. It was thought that he was bleeding from an arteriosclerotic vessel in a diverticulum, probably of the sigmoid. His hemoglobin rose to 8 gm. with 2,870,000 red blood cells. He received 500 c.c. more of blood, making a total of 2,500 c.c. Following the 5th transfusion, blood disappeared from his stools and he gradually became alert and well oriented. X-ray of the colon showed numerous diverticula present along the sigmoid flexure associated with spasm. He was discharged after 28 days in the hospital with a hemoglobin of 9.5 gm. and a red blood cell count of 3,550,000.

*Comment:*—In this case the blood pressure seemed good on admission but the patient was semi-stuporous, and blood transfusion effected an improvement in his condition. Recurrence of bleeding responded to further transfusions.

#### DISCUSSION

All of the cases reported were admitted to Queens General Hospital, Jamaica, N. Y. There were 131 admissions for diverticulitis and diverticulosis of the colon during the 3½ year period starting January 1, 1950 and ending June 30, 1953. Of this group, there were 37 with gross rectal bleeding, an incidence of 28 per cent. These included 14 cases (10 per cent) of massive rectal hemorrhage which form the basis for this report.

There were 10 males and 4 females, a ratio of 2½ to 1. Their ages varied from 64 to 83 years. Five were in the sixth decade, six were in the seventh decade and three were in the eighth decade. The amount of blood required varied from 500 c.c. in six cases to 2,500 c.c. in two cases. The duration of the hospital stay varied considerably, depending upon the initial severity of the hemorrhage, the number of recurrences, the response to therapy and the presence of complications. The lowest hemoglobin (3 gm.) occurred in case 1 in which the blood pressure was 150/60 mm. Hg. The highest hemoglobin of 14 gm. was found during the third admission of case 4 whose blood pressure was reported as 100/60 mm. Hg. The white blood count varied from 5,000 to 24,200. The temperature was elevated (102°F.) in only one patient (Case 2) who died of coronary occlusion and myocardial infarction five hours after admission. The diverticula were found in the sigmoid alone in four cases or 28 per cent, in the sigmoid in addition to other parts of the colon in ten cases or 71 per cent, the findings in this group of cases agreeing very closely with the location of diverticula of the colon as reported in the literature. The liver was enlarged in six cases (Cases 1, 2, 6, 10, 13 and 14) but as far as can be ascertained liver dysfunction played no role in the pathogenesis of the bleeding. In none of the cases in which liver function tests were performed was there reversal of the albumin/globulin ratio, a lowered percentage of prothrombin activity or other evidence of liver disease.

These cases were selected because there was no doubt as to the massive character of the rectal bleeding. All of the patients lost a substantial amount of blood and one or more transfusions were necessary to replace the blood loss. The latter was associated with symptoms of shock, such as weakness, syncope or exhaustion and followed by evidence of blood loss as shown by pallor, lowered blood pressure, and low hemoglobin. The hemoglobin level or red blood cell count at the time of admission was not too reliable an index of the amount of blood lost. When extensive blood loss occurred over a long period of time, the symptoms were not as severe as when a smaller amount of blood was lost over a short period. In addition the personal element was an intangible but important factor, for some patients displayed symptoms of shock with relatively slight blood loss while others were symptom-free after the loss of much larger amounts of blood.

While some of our patients gave the usual history of diverticular disease, with recurring attacks of lower abdominal pain and constipation interrupted by occasional attacks of diarrhea, others had no previous history of such illness. The onset of hemorrhage was the first indication of their disease. In this group some had accompanying abdominal crampy pain while in others the hemorrhage was completely painless.

The sudden appearance of a sizable amount of blood from the rectum throws the elderly patient into a state of fear and confusion. The physician is left with the responsibility of making an accurate diagnosis so that the treatment may be as prompt as possible. Malignancy of the gastrointestinal tract must be given first consideration in every case. Although x-rays are not taken in the presence of shock, x-ray examination may be performed when the patient's condition has improved even though there is some bleeding present.

There is no doubt of the presence of a varying degree of generalized arteriosclerosis and circulatory insufficiency in the age group reported, as shown by the frequent diagnoses of arteriosclerotic or hypertensive heart disease and enlarged heart, and the history of cerebrovascular accidents. There is evidence to show that arteriosclerosis alone may be responsible for massive rectal hemorrhage<sup>12</sup>. The abdominal aorta is often the site of atherosclerosis and the smaller vessels may also be involved. Wartman<sup>13</sup> has shown that marked arteriosclerotic changes occur in the vessels of the gastrointestinal tract in about 33 per cent of people over 60 years of age. These may be some of the people in whom the presence of diverticula leads to episodes of bleeding. In many cases the bleeding may be caused by separation of a brittle arteriosclerotic plaque from a small artery in close relation to a diverticulum. Such an occurrence can be precipitated by a sudden increase in intraabdominal pressure such as is caused by the taking of a laxative.

It must also be remembered that other sources of bleeding may coexist with the presence of diverticula<sup>14</sup>. Carcinoma may be present, or a hemangioma or

other tumor may be the site of the bleeding. In patients with repeated massive hemorrhage surgical exploration may be rewarding at the time of recurrence of active bleeding.

In addition to the administration of blood and fluids in the cases presented, the treatment was supportive and symptomatic. Medication consisted of sedatives to relieve apprehension and restlessness, and demerol or morphine for the control of pain. Iron and vitamins were given as indicated. Digitalis and mercurials were given when necessary for cardiac conditions and congestive failure. Antibiotics were administered when deemed advisable.

#### SUMMARY

1. Fourteen cases of massive hemorrhage due to diverticula of the colon are reported.

2. Rectal bleeding is a frequent presenting symptom in patients with diverticula of the colon. The percentage of gross rectal bleeding over a 3½ year period was found to be 28 per cent. Massive hemorrhage occurred in 10 per cent of the cases.

3. Massive rectal hemorrhage looms as an increasingly important problem in an aging population. Recognition of its association with colonic diverticula is necessary for proper treatment, which is primarily medical although surgical exploration may be indicated for recurrent massive hemorrhage.

4. The presence of an elevation of temperature should make one suspect a medical or surgical complication.

5. Arteriosclerosis and hypertension are common incidental findings in patients with hemorrhage due to diverticula, and their role in the etiology of the bleeding may be an important one.

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# CLINICAL AND BACTERIOLOGICAL STUDIES OF A NEW LACTOBACILLUS ACIDOPHILUS CONCENTRATE IN FUNCTIONAL GASTROINTESTINAL DISTURBANCES\*

## PRELIMINARY STUDY

HENRY A. RAFSKY, M.D., F.A.C.P., F.A.C.G.†

and

JEANNE C. RAFSKY, M.D.

New York, N. Y.

The concept that the bacterial flora of the intestines plays an important part in maintaining the function and integrity of the gastrointestinal tract has survived mistaken theories, over-optimistic expectations of therapy, and a multitude of unsatisfactory lactobacillus preparations. Recent adverse experiences with the broad-spectrum antibiotics have reemphasized the significance of bacterial equilibrium and the favorable influence of certain lactobacilli in counteracting overgrowth of harmful organisms and in preserving normal intestinal hygiene<sup>1-10</sup>.

Metchnikoff's early hypothesis that good health and long life were peculiarly dependent on the intestinal population of lactobacilli is no longer accepted<sup>11-14</sup>. His emphasis on the unique value of *Lactobacillus bulgaricus*, a yoghurt milk culture morphologically resembling the fecal strains of lactobacilli found in the healthy aged who consumed yoghurt, has proven misdirected, since this organism is foreign to the human intestinal tract and will not survive in it. Beneficial results were largely due to the stimulation of native acidophilus strains by the associated high lactose intake. The long-term studies of Rettger and his group<sup>11</sup> demonstrated, however, that in certain functional disorders of the gastrointestinal tract, such as the irritable colon, diarrhea, constipation, and colitis of diverse etiology, the administration of an acidophilus milk, containing high numbers of viable *Lactobacillus acidophilus* of a human strain, affords positive results in many cases which had failed to respond to all other treatment. Significantly, they reported that in a large proportion of instances, the clinical benefits were maintained even after cessation of therapy. Additional studies<sup>1,2,15-17</sup> increased our appreciation of the therapeutic potentialities of *L. acidophilus*.

Nevertheless, in recent years clinicians have not generally been enthusiastic about *L. acidophilus* therapy, primarily because of drawbacks in the types of preparations available and their patients' reactions to them. In order to be effective, acidophilus products should contain on ingestion not less than 100

\*The stool cultures were done by Dr. Perry J. Manheims at the Lenox Hill Hospital, New York, N. Y. The material used in this study was supplied as Viacil tablets (Viable *L. acidophilus* Borden's) through the courtesy of the Prescription Products Division of The Borden Company.

†Deceased.

million organisms per c.c. of acidophilus milk or per gram of concentrate. The recommended daily dose is 100 billion viable organisms per day. Many technological factors have interposed difficulties in the way of achieving a standardized product of dependable potency and viability.

Rettger et al<sup>11</sup> stated: ". . . we wish to stress the importance of taking every precaution in the preparation, distribution and storing of acidophilus milk, to furnish a product of high viability, as well as purity, and to maintain these properties in the finished product over appreciable periods of time . . .".

Failures in acidophilus therapy have usually been attributable to inadequate intake of viable lactobacilli of the right type or to clinical application in non-functional disorders.

From the viewpoint of the patient, too, there have been grounds for dissatisfaction, notably in regard to the bulk, the acidity, taste, and, for milk-sensitive individuals, the potentially allergenic effects of a milk preparation. Even in tablet form, there has not been a product available which could be conveniently administered in the necessary massive dosage. For one such preparation, for example, it has been calculated that tons of the material would be required to match ordinary milk culture dosage<sup>12</sup>.

For these reasons, when a new *Lactobacillus acidophilus* preparation became available, furnishing in three ordinary-sized tablets not less than 100 billion viable *L. acidophilus* organisms of a human intestinal strain, a renewed attack on the problem of effective acidophilus therapy in gastrointestinal disorders seemed warranted. Developed by a special process which protects the organisms against destruction in the stomach and sustains their viability, this preparation seemed to fulfill the hopes of the original investigators for an acidophilus preparation, which could supply in small bulk the requisite count of *L. acidophilus* in a form which would be viable over "appreciable periods of time". This preliminary report describes our experience with Viacil\* in the relief of gastrointestinal distress and dysfunction associated with irritable colon and diverticulosis.

#### CLINICAL MATERIAL AND METHOD

This series consisted of 39 patients, of whom 18 were males and 21 females; their ages ranged from 39 to 70 years. Thirty-one patients manifested an irritable colon and 8 were suffering from diverticulosis. The patients' chief complaints were lower abdominal pain, which at times became quite severe and radiated posteriorly, and an accumulation of gas, especially at night. In 17 of the patients, constipation was also present; in 11 diarrhea was a complaint; in 5 alternating attacks of constipation and diarrhea were prominent symptoms. Three gave a history of food allergy.

\*The Borden Company, New York, N. Y.

The usual dosage was one tablet three times daily, accompanied by one heaping teaspoonful of beta lactose. Sometimes, patients would take 2 tablets and 2 teaspoonfuls of the beta lactose in the morning and one tablet and one teaspoonful of the lactose in the evening. Duration of treatment extended from a minimum of three months to a maximum of ten months. Stools were examined for viable *L. acidophilus* before and periodically after the patients were placed on the therapy.

### RESULTS

**Clinical:**—In 32 of the 39 patients, clinical improvement was noted within one to three weeks after the medication was started. At the outset, some patients noted an increase in the accumulation of gas, but this, as a rule, disappeared on continuation of treatment. The abdominal distress subsided or was markedly relieved; there was less formation of gas; the appetite improved; and the patients showed improvement in body weight. They stated that their "nights were more comfortable".

**Bacteriological:**—Upon examination of the stools, we found that at times we could culture a good growth of *L. acidophilus* colonies after the patients had taken the medication for two weeks. On the other hand, we were not always able to isolate the organism even though the patient took medication regularly for longer intervals. There was no definite bacteriological pattern which we could observe in relationship to the dosage, the length of time the medication was given, or the clinical improvement. This is not surprising in view of Rettger's observation that clinical improvement was not necessarily associated with fecal evidence of implantation.

### CASE REPORTS

The following cases, which had previously been among the most refractory, will illustrate the results obtained in patients with an irritable colon and with diverticulosis when treatment with *L. acidophilus* tablets and beta lactose was employed:

**Case 1:**—J. K., a white, 53-year old male, had periodic attacks of severe lower abdominal pain. He frequently complained of diarrhea and gave a history of food allergy. A cholecystectomy had been performed about 2½ years ago for cholelithiasis. This operation did not relieve his bowel symptoms. The patient stated that inability to sleep nights on account of "gas" was his chief annoying symptom. He was thoroughly investigated and all that could be found was an irritable colon. Before he was seen, he had tried several antispasmodics, sedatives, and various dietetic regimens without success. He was finally placed on the *L. acidophilus* tablets, with beta lactose. He began to show evidence of clinical improvement after 3 weeks and has continued to show improvement. He suffers a relapse periodically whenever he is under a severe emotional strain or commits

a dietary indiscretion, but these relapses subside readily. The patient's pain is under much better control, his nights are more comfortable, and he has steadily gained weight. He has been on the medication for ten months.

*Case 2:*—L. F., a 51-year old female, complained of severe pain in the lumbar and sacral regions, radiating to the rectum, from which she had suffered for seven years. She was constipated and also stated she had been troubled with intestinal gas which she was unable to expel. Numerous examinations had been made because she insisted that she had a malignancy, but nothing could be found but an irritable colon. As in the previous case, sedatives and a variety of antispasmodics were unable to give relief. Other forms of medical therapy and diets were also employed. The patient felt no better. She consulted a psychiatrist but after a period of time discontinued this form of treatment. She was then placed on the *L. acidophilus* tablets and beta lactose therapy and in one month's time began to note improvement. She complained of somewhat more gas at the beginning of the treatment but this became less as time went on. The patient has been on the medication for 6 months. When last seen, she stated she felt markedly improved.

*Case 3:*—W. T., a 70-year old, white, male, had complained of periodic attacks of lower abdominal pain, especially over the left lower quadrant, for about 4 years. The attacks did not come on with any regularity. He could not attribute them to any indiscretion in diet. When the attacks came on, he stated he was unable to pass any gas and he was most uncomfortable. Various examinations showed a diverticulosis in the region of the sigmoid. The patient stated that no drugs ever helped him. We persuaded him to give the acidophilus concentrate and beta lactose therapy a trial. At first he stated the medication increased the gas but he continued the treatment; after 3 weeks he said he really felt better. As soon as he did improve he would discontinue the therapy, with some recurrence of symptoms, and when he renewed the medication he again showed signs of marked clinical improvement.

#### COMMENT

Our experience with a new tablet concentrate of *Lactobacillus acidophilus* in long-standing and refractory cases of functional intestinal disorders seems to indicate that the improvement noted is not psychic but actual. Thus, three of our patients were being treated by psychiatrists without benefit before they started the acidophilus therapy. Others had been under all kinds of therapy without success. Furthermore, when some of our patients felt better and discontinued the medication, the symptoms would return. After they were put back on the therapy for a few weeks, they would improve again.

We believe that the initial increase of gas in our patients was produced by the fermentation of the added carbohydrate administered with the medication.

It should be emphasized that the effectiveness of this form of therapy is dependent on proper dosage and regularity of treatment. Patients must be cautioned against interrupting therapy too soon.

#### SUMMARY

1. A series of 39 patients were treated for irritable colon (31 cases) or diverticulosis (8 cases). Therapy consisted of oral administration of a viable human intestinal strain of *L. acidophilus* in the form of a tablet concentrate providing 100 billion viable organisms per daily dose (3 tablets in divided doses). Beta lactose was also given (one teaspoonful per tablet). Treatment lasted not less than three months and in the longest course was continued for 10 months.

2. Clinical improvement, consisting of relief of pain, gas, constipation, and diarrhea, was observed in 32 of the 39 cases (82 per cent), within one to three weeks. The therapy was gratifyingly effective in long-standing cases which had resisted other measures, including psychiatric.

3. There was no discernible bacteriological pattern in relation to dosage, duration of treatment, or clinical improvement. Hence, there are many bacteriological and clinical aspects to this problem which should be studied further.

#### CONCLUSIONS

1. Oral administration of a human intestinal strain of viable *L. acidophilus* in a new concentrate providing 100 billion viable organisms per daily dose of just 3 tablets has a distinct place in the treatment of certain gastrointestinal disorders such as refractory irritable colon and diverticulosis. The simplicity and convenience of the treatment are especially advantageous.

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## PNEUMOPERITONEUM, A DIAGNOSTIC AID

N. B. JAFFE, M.D., F.A.C.G.

Bridgeport, Conn.

Pneumoperitoneum, as a vital factor in therapeusis of phthisis, and possibly of equal curative value in various abdominal pathologies is a well established procedure. It is also of notable advantage in diagnosis of abdominal and pelvic problems. Recently, it assumed a formidable role in clarifying sex endocrine anomalies, especially in children and others, due to the difficulty of adequate pelvic examination.

Conditions as ovarian agenesis, pseudohermaphroditism, precocious puberty, hypo-ovarianism, cystic ovary and many other rare anatomic deviations, can be clarified by pneumoperitoneum, followed by x-ray.

Perirenal air insufflation may reveal the presence of a pheochromocytoma. Visualization of the liver is greatly enhanced because of the rise of the right dome of the diaphragm. The pressure of the injected air, and the diminution of the negativity of the subdiaphragmatic pressure also produces better visualization. A comparison of the highest point of the spleen with that of the liver during treatment, suggests that there exists a relationship between the rise of the left dome of the diaphragm and the lienoptosis, similar to that between the rise of the right dome of diaphragm and hepatoptosis. No other process enables us to visualize the spleen as does the air distention of the abdominal cavity.

Roentgenologic diagnosis of tuberculous enterocolitis, hyperirritability, filling defects, hypertrophic circular areas, partial obstruction, vascular images, rough and serrate appearances, obliteration of hastrations, are better seen after pneumoperitoneum.

Pneumoperitoneum, facilitates the diagnosis of pelvic diseases by introduction of gynecologic pneumoroentgenography, and so many eliminate exploratory laparotomy. The injection of 1,000-1,200 c.c. of oxygen or air, sometimes with iodized oil, may demonstrate the relationship of the uterine cavity and the tubes, in a large pelvic mass. Enlarged, thickened, tortuous fallopian tubes reveal dense shadows on the film. Calcium deposits in the wall of the tubes can be easily demonstrated.

Pneumoperitoneum should be applied in conjunction with other clinical and laboratory procedures, in those instances in which the diagnosis is obscure. It may confirm clinical impressions when other data are not sufficient for a convincing diagnosis; or it may completely change the clinical impressions. It is a superb method, enabling the radiologist and clinician to study the outlines of the abdominal and pelvic viscera.

Pelvic pneumoperitoneum enables one to differentiate on the film between normal and abnormal pelvic conditions. It reveals the type of pathological ovarian swelling, absence or presence of the uterus, ovarian and tubes in the absence of the vagina. In the child and adolescent, or virgin adult, digital examination may be impossible or impractical. Under these circumstances pneumoperitoneum is of special value to reveal pelvic anomalies and pathologic conditions. This is very advantageous when a diagnosis cannot be ascertained without a laparotomy, and when laboratory procedures are doubtful.

According to Benayi, artificial pneumoperitoneum has been found useful in the diagnosis of abdominal diseases, particularly for the purpose of visualizing the contour, size and position of the liver and spleen. Also, it may enable one to determine the presence or absence of tumors, peritoneal effusion and adhesions. It is of assistance in deciding whether a basal thoracic shadow signifies disease below or above the diaphragm. Pneumoperitoneum is of immense value, with or without the instillation of iodized oil, in gynecological diagnostic work. It is of course indicated prior to peritoneoscopy.

Kunstadter, Guterman and Tulsky, in a recent, excellent publication, elucidated masterly the great diagnostic worth of pneumoperitoneum in sex endocrine anomalies and physiology. In their series of 16 cases, there were seven ovarian agenesis; one primary hypopituitarism; two hypo-ovarianism (pituitary); one cystic ovary; two sexual precocity; three pseudohermaphroditism—13 females; two males and one of undetermined sex.

Before inducing pelvic pneumoperitoneum, the following should be done: complete laboratory analysis, hormone excretion as 17-Letosteroids, and urinary pregnanediol, vaginal smear for estrogen activity; x-ray studies, cella turcica, bone age, perirenal air insufflation, endometrial biopsy, measurements; weight, height, span, symphysis-vertix, symphysis-sole.

The technic is not difficult. It is contraindicated during active intraperitoneal inflammation, systemic infection, cardiac and respiratory embarrassment.

The horizon of diagnosis is constantly widening. Every advance in this sphere is a triumph over the intricacies of natural forces. Pneumoperitoneum is an excellent procedure, of the utmost worth, revealing anatomic abnormalities, pathologic obscurities, into the clear region of reason, and scientific realm.

## EDITORIAL

### RIGHT LOWER QUADRANT PAIN AND ITS DIAGNOSTIC SIGNIFICANCE

Acute and chronic affections occurring in the right lower abdomen are often baffling and require a careful and detailed history and a more careful differential diagnosis. There are many obscure conditions found in the lower right quadrant of the abdomen and the physician must bear in mind the immediate and remote organs which may give rise to acute or chronic pain in this area. Pain and tenderness does not always signify an appendicular involvement and removal of this organ, as it often happens, may still leave the patient with his pain.

Many physicians regard the right iliac fossa as a legitimate hunting ground and rather than attempt to find the exact cause of distress, advocate removal of the appendix in the hope that the patient will be relieved. Many times the real cause of the distress is functional as in gaseous or soft fecal retention in the cecum, or a general spasm of the entire viscera including the colon. Malignancy of the colon including the cecum seldom manifests pain in the early stages. Typhlitis and perityphlitis, almost unknown by the younger physicians, may often cause pain and tenderness in the right iliac fossa.

Regional ileitis, tuberculosis, lymphadenopathy, the latter more frequent in children after throat infections, may be a source of pain in this area. These mesenteric enlarged ileocecal glands are often felt by the examiner and are painful on palpation. They can, however, be differentiated from appendicitis by changing the position of the patient, but there is no shifting of the pain. There is absence of true muscular rigidity and vomiting is of rare occurrence. Tuberculous adenitis is more difficult to diagnose, although a positive Mantoux reaction in younger children is rather in favor of tuberculosis. X-ray examination is of little value, while a careful study of the stool may help in the differentiation, especially when a pale fatty stool is found, which undoubtedly is due to blockage of the lymphatic vessels.

Other causes of pain may be due to acute and chronic pyelitis, pyelonephritis, hydronephrosis, Dietel's crisis, stone in the right ureter, stones in bladder, prostatic infections and inflammations in males, vesiculitis right, architis, hernia. In adolescent girls and married women, gynecologic conditions are fairly common: various menstrual disorders, midmenstrual pain due to blood seeping into the peritoneal cavity, ovarian and tubal inflammations, ruptured graafian follicle, cysts, right-sided ectopic pregnancy in the early stages and after rupture.

Bleeding into the peritoneal cavity from a ruptured graafian follicle or corpus luteum occur most frequently in the late teens or early twenties. Although no specific relation to occupation can be determined, the frequency is almost twice as great for unmarried as for married women. Trauma on exertion does

not seem to be a causative factor; the pain occasionally may start during sexual intercourse.

The chief symptom caused by a bleeding ovary is pain which ordinarily begins and persists in the lower abdomen, most frequently on the right side and is usually more severe than in appendicitis. A great many patients recall that the pain began in the epigastrium, later localizing in the right lower quadrant; shoulder pain occurs rarely, even when fluid extends upward and produces diaphragmatic irritation. Nausea, present in most cases, is accompanied by vomiting in about 25 per cent of the patients.

Although right lower quadrant tenderness is found in almost nine-tenths of the patients, only about one-fourth have definite associated muscle spasm. Adnexal tenderness is frequently found on pelvic examination, but a mass is seldom palpable. Leucocytosis usually occurs, though seldom to a great extent, and the temperature is rarely elevated above 101° F., with only slight increase in pulse rate.

Preoperative diagnosis is difficult, although the relation of pain in the abdomen and the rupture of a graafian follicle midway in the menstrual cycle is an important clue in differentiation. Bleeding from the ovary, not associated with ovulation, may be caused by rupture of a corpus luteum or a corpus hemorrhagicum or a retention cyst of the ovary, with bleeding from the ovarian surface at the time of a menstrual period. At operation, the surgeon may find an accompanying acute inflammation of the appendix or a Meckel's diverticulum.

Various spinal conditions, such as congenital or acquired deformities and arthritis, Patti disease, a psaos or tuberculous abscess may also reflexly give rise to pain in the right lower quadrant.

Children with pneumonia involving the right lower lobe may have reflex pain in the right iliac fossa.

SAMUEL WEISS, M.D., F.A.C.G.

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## In Memoriam

We record with profound sorrow the passing of Dr. William L. Wolfson, Fellow, of Brooklyn, N. Y. We extend our deepest sympathies to the bereaved family.

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## *President's Message*

It is time to turn our attention to our Annual Meeting in Chicago at the Shoreland Hotel and to lay out the time so that we can arrive early. Your officers have been focusing their efforts on the event for many months. We will try an innovation this year because the shortage of time has seemed to demand it. The Convocation will be held on Sunday evening, 23 October. It is an event that requires ample time, reflection, and dignity. For that reason when you set up your reservation, plan to arrive early Sunday afternoon, get acquainted and be present at the Convocation.



The Annual Convention will be one of the finest thus far. An excellent program has been arranged using a splendid group of men from that great medical center augmented by talent from all over the United States. The Postgraduate Course which follows is designed to review and teach gastroenterology in detail as it should be practiced. Those attending will be given credit toward advancement not only in our own organization but in allied fields. It is my hope that sometime we may set up some type of required postgraduate educational program similar to that used by the Academy of General Practice. I feel certain that it would be beneficial to our organization.

Mrs. Joseph Shaiken, chairman of arrangements for the Ladies' Auxiliary, has put considerable thought and effort into arranging entertainment for the ladies which we think will prove enjoyable and worthwhile. Mrs. Kaplan, the Corresponding Secretary will mail a schedule of events to the membership. Many of your ladies are not, as yet, members of the Auxiliary. They will be most welcome.

Your officers like to know what you think. They will appreciate well thought-out suggestions geared to our national level. Let's work to improve our College but at the same time keep humble and human in the interest of good medicine.

A handwritten signature in cursive script, appearing to read "Lynn A. Ferguson".

## NEWS NOTE

### COURSE IN POSTGRADUATE GASTROENTEROLOGY

The American College of Gastroenterology announces that its Annual Course in Postgraduate Gastroenterology will be given at The Shoreland in Chicago, Ill., on 27, 28, 29 October 1955.

The Course will again be under the direction of co-chairmanship of Dr. Owen H. Wangensteen, Professor of Surgery of the University of Minnesota Medical School, who will serve as surgical co-ordinator and Dr. I. Snapper, Director of Medical Education, Beth-el Hospital, Brooklyn, N. Y., who will serve as medical co-ordinator. Drs. Wangensteen and Snapper will be assisted by a distinguished faculty selected from the medical schools.

The subject matter to be covered in the Course, from a medical as well as surgical viewpoint, will cover, essentially, the advances in diagnosis and treatment of gastrointestinal diseases and a comprehensive discussion of diseases of the mouth, esophagus, stomach, pancreas, spleen, liver and gallbladder, colon and rectum, with special studies of radiology and gastroscopy.

For further information and enrollment write to the American College of Gastroenterology, 33 West 60th Street, New York 23, N. Y.

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### GASTROINTESTINAL TRACT

#### THE DIAGNOSTIC VALUE OF PAIN IN NONPENETRATING ABDOMINAL INJURIES: Chester C. Guy. *Illinois M. J.* 107:62 (Feb.), 1955.

Nonpenetrating abdominal injuries involve the lower thoracic and abdominal wall, the solid and the hollow viscera. Pain of the former is usually severe, of the latter mild or absent unless peritonitis supervenes. Injuries to the lower chest wall interfere with respiration and are frequently associated with damage of liver or spleen. Trauma of abdominal wall may mimic internal injury especially if a deep hematoma occurs which might be mistaken for an intraabdominal mass. Liver injuries are usually treated conservatively because if they are minor they heal spontaneously, if they are severe they are usually fatal regardless of conservative or surgical treatment. Traumatic bile peritonitis with bradycardia and jaundice may require surgical drainage. Injury to the pancreas is conservatively treated unless pseudocyst occurs. Ruptured

kidneys are associated with severe pain due to urinary leakage, early therapy is conservative. Ruptured spleen is a surgical disorder under all circumstances. Fulminating hemoperitoneum occurs rarely, while a slowly growing perisplenic hematoma is the rule. Posttraumatic pains in the splenic region should be watched closely. Injuries of the hollow viscera require early surgical interference. The stomach is rarely torn but rupture of the retroperitoneal wall of the duodenum is not uncommon. Small bowel injuries cause severe hemorrhage and peritonitis, but hardly ever pneumoperitoneum, those of the colon usually show subdiaphragmatic air but are less irritating, especially, the more frequent ones restricted to the left half of the colon.

H. B. EISENSTADT

#### THE ACUTE ABDOMEN—DIAGNOSIS AND TREATMENT: R. Richard Renner. *Ohio M. J.* 51:226 (Mar.), 1955.

The author stresses the importance of early diagnosis and treatment of the most common conditions causing the acute abdomen. He gives us his own views on management of the acute abdomen which serves as a good review for those of us who do not get to see the acute abdomen too often.

It is important to remember that death may still occur from a ruptured appendix in spite of our 'magic' antibiotics. For this reason one must give attention not only to the early diagnosis, but also to the early treatment of the acute abdomen.

ABE ALPER

#### INTESTINAL OBSTRUCTION: Philip Thorek. *Clin. Med.* 2:267 (Mar.), 1955.

Intestinal obstruction is a symptom complex so that other information is essential for an early and thorough understanding of the pathology.

Often the triad of distention, obstipation and vomiting will be a diagnostic lead. A

way of testing distention is recognizing that the undistended umbilical relationship is at a lower horizontal level than the xiphoid, but that with distention the umbilical level is above the xiphoid. The umbilical level should be recorded on ad-

mission followed by a recheck every hour. Most obstruction patients pass neither feces nor flatus, but in incomplete obstruction such as in Richter's hernia, the irritation gives rise to hyperperistalsis and possibly diarrhea. One pathognomonic finding in obstruction is the simultaneous appearance of pain and intestinal sounds, which differentiates intestinal colic from other pains.

Treatment of obstruction is based on six types of therapy. Suction has lowered the mortality but it has no place in colonic obstruction, nor where there is strangulation. Saline prolongs life by maintaining the chloride ion lost by vomiting and suction.

Whole blood is used only when red-blood cells are lost. The protein balance, which must be maintained, is regulated by use of plasma, serum, or amino acid therapy. Too little protein and too much chloride produce tissue edema. The patient must be supplied with vitamins.

Immediate surgery is indicated in strangulation. Complete nonstrangulated colon lesions require immediate colostomy.

Early ambulation is practiced with active and passive motion as well as breathing exercises. The patient is gotten out of bed on the first postoperative day.

REGINALD B. WEILER

## ESOPHAGUS

### CARDIOSPASM: G. M. Brownrigg. *Canad. M.A.J.* 72:104 (15 Jan.), 1955.

Four cases of cardiospasm (achalasia, cardiosophageal dystonia) are reported, which were treated successfully by extramucosal myotomy. Treatment for cardiospasm is either medical (dilatation by instrumental or other means), or surgical (cardioplasty, resection or myotomy). Myotomy, which has gained acceptance in Europe, is the procedure of choice. Myotomy is similar to the Ramstedt procedure for congenital pyloric stenosis. A transthoracic approach is advocated, with division of the muscle fibers of the lower esophagus and cardia until the mucosa is exposed. The

author reports four cases of cardiospasm treated in this manner with immediate relief of symptoms. Although each case presented the clinical and radiological findings of cardiospasm, at operation there was no dilatation of the esophagus and no hypertrophy of the muscle. Yet in each case division of the muscle fibers led to complete relief. Therefore negative findings at operation should not deter the surgeon from carrying out his task. Transthoracic exposure also allows early detection of resectable neoplastic lesions in this area.

ARNOLD STANTON

## STOMACH

### THE TREATMENT OF PEPTIC ULCER WITH LICORICE EXTRACT: K. Neidhardt and W. Schmucke. *Deutsche med. Wochenschr.* 80:251 (18 Feb.), 1955.

The evaluation of the efficacy of any drug in peptic ulcer disease is extremely difficult because 40-50 per cent of all ulcers verified by clinical and roentgenological means heal spontaneously. A still larger number of cases never reach the physician and get well. If these fundamental experiences are neglected claims for the curative effect of any treatment for ulcer can be made.

Thirty hospitalized ulcer patients received each 40 grams of licorice extract daily, dissolved in one glass of water, taken in broken doses during the entire day. In addition, the basic ulcer treatment consisting of diet, rest and a minimum of conventional drugs to relieve the symptoms were prescribed. Sixty-three per cent of these patients were clinically and roentgenologi-

cally cured. However, 85 per cent of the 54 controls receiving only the standard treatment were also cured. These results, even if obtained only on a relatively small number of persons, indicated that the addition of licorice extract to the standard ulcer therapy does not influence the cure rate. Ambulatory licorice treatment, without standard rest treatment, had a much less favorable result than the standard hospital therapy alone. Recheck of all patients six months after therapy showed the same recurrence rate for those persons treated with and without the licorice extract. The authors come to the conclusion that licorice therapy is ineffective both in hospitalized as well as ambulatory patients.

H. B. EISENSTADT

**GASTRIC ULCER AND GASTRIC CANCER: Calvin M. Smyth. Pennsylvania M. J. 58:209 (Feb.), 1955.**

The relationship of gastric ulcer and gastric cancer is again reviewed in the light of surgical vs. medical management. The author is of the opinion that the differential diagnosis between benign ulcer and cancer of the stomach cannot be made by the internist, the radiologist, the gastroscopist and or even by the surgeon at the time of operation. Gastric ulcer is a surgical disease and, with the possible exception of the superficial ulcers which heal completely in

a matter of days to a week or two, should not be treated medically. The term "peptic ulcer" should be discarded as it leads to the false idea that gastric and duodenal ulcer are the same. Since positive differentiation between benign and malignant ulcer cannot be made by any methods presently available, the surgeon at the time of operation for ulcer should operate with the idea that he may be dealing with cancer.

LOUIS A. ROSENBLUM

**LIVER AND BILIARY TRACT****LIVER FUNCTION STUDIES: B. B. Elster and H. B. Eisenstadt. Texas J. Med. 51:18 (Jan.), 1955.**

This study was undertaken to determine the possible toxic effects upon the liver of Dicumarol in anticoagulant therapy.

In animal experiments a great variety of liver abnormalities from fatty infiltration to necrosis of the central parenchyma is noted after relatively small doses of Dicumarol were given for a short period of time.

The authors conducted liver function tests in patients subjected to Dicumarol therapy for 6 to 60 months and concluded that so far in their chemical study there is no conclusive evidence of hepatic damage in their series of 35 patients.

H. M. ROBINSON

**BILIGRAFINAUSSCHEIDUNG IM HARN ALS CHROMODIAGNOSTICUM FÜR DIE LEBERFUNKTION: H. Witzgall and U. Trebbin: Arztliche Wochenschr. 10:178 (25 Feb.), 1955.**

Intravenous tetraiodophenolphthalein, introduced by Graham and Cole, combined x-ray visualization of the gallbladder with liver function testing. Because such a combined procedure simplifies clinical examinations the possibility of using intravenous Biligrafine (Cholografine, 20 c.c. of a 20 per cent solution) for hepatic chromodiagnosis in addition to cholecystography was investigated. Any contrast medium of the gallbladder must have the following properties to be concomitantly useful for liver function study: It must be well tolerated, parenterally administered, inabsorbable from the gastrointestinal mucosa (in order to exclude enterohepatic circulation), not metabolized in the body, mainly excreted by the liver and preferably also somewhat by the kidneys, with a fixed relationship between hepatic and renal excretion. Biligrafine fulfills these requirements in an excellent way. In normal persons 90 per cent of the dye is removed by the liver, 10 per cent by the kidneys. This requires several days but most of the material is excreted during the

first 24 hours. Any hepatic dysfunction will lead to a decrease of the amount of dye eliminated by the liver with a corresponding increase of its renal clearance. Healthy persons eliminate 8 per cent or less of the Biligrafine during the 24 hours following its intravenous injection in their urine. Values above 15 per cent and probably already above 12 per cent are abnormal. Values between 8-12 per cent are suspicious of mild hepatic dysfunction. If x-ray visualization of the gallbladder does not occur the urine examination for Biligrafine (for its iodine contents) will immediately show if this is caused by a gallbladder or liver dysfunction. A comparison of the Biligrafine excretion with other liver function studies shows best agreement with serum bilirubin elevation and BSP retention, however, the former test returns to normal more quickly in case of a clinical recovery. Renal failure and dysproteinemia interfere with the urinary Biligrafine excretion while it is independent from water diuresis.

H. B. EISENSTADT



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1. Balfour, D. C., Jr.: Am. J. Gastroenterol. 22:181, 1954.  
 2. Burke, J. O., et al.: Internat. Rec. Med. & Gen. Practice Clin. 167:587, 1954. 3. Sternberg, S. D., and Greenblatt, I. J.: Ann. Allergy 9:198, 1951.

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# Pamine\* Phenobarbital BROMIDE

# Elixir

*Each 5 cc. (approx. 1 tsp.) contains:*

Phenobarbital .....	8.0 mg. ( $\frac{1}{8}$ gr.)
Methscopolamine bromide .....	1.25 mg.
Alcohol .....	20%

*Dosage:*

1 to 2 teaspoonfuls three or four times daily, depending upon requirements in the individual patient.

*Supplied:* Pint bottles.

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*Thank You*

We thank you, doctor, for prescribing Trevidal. Most of you who have employed this new, balanced protective antacid have continued to use it routinely. For those of you who have not yet had a chance to evaluate the unique antacid activity of Trevidal, may we suggest you write us today for a clinical trial supply.

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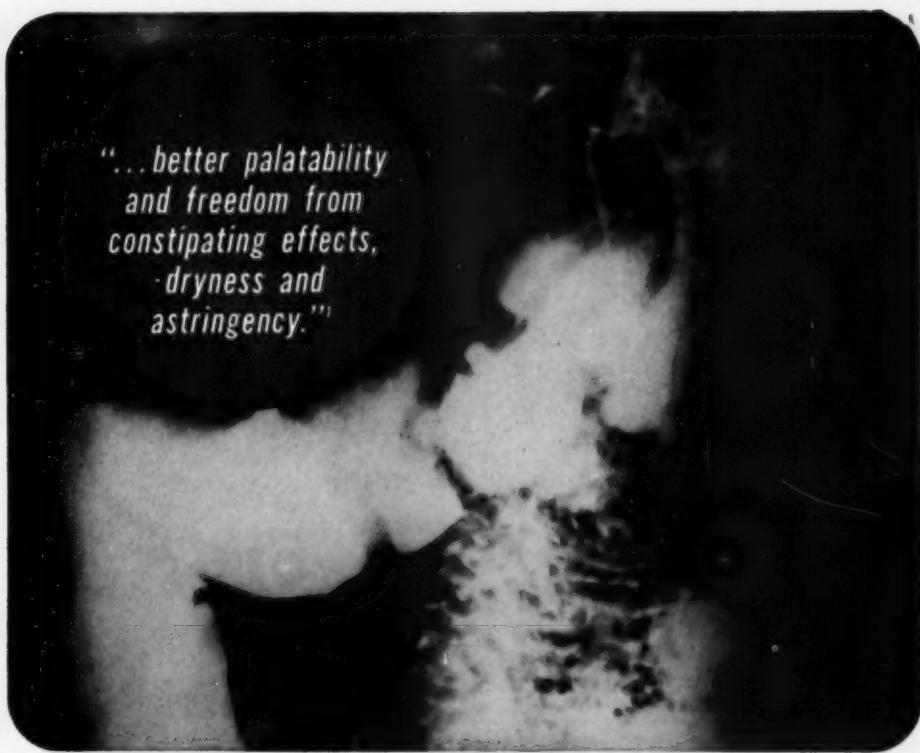
Unique vegetable mucin supplies protective coat to irritated stomach lining	Regonol*‡ . . . . .	100 mg.
Balance of ingredients avoids constipation, diarrhea, or alkalosis	Magnesium trisilicate . . . . .	150 mg.
	Aluminum hydroxide gel . . . . .	90 mg.
	Calcium carbonate . . . . .	105 mg.
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Binder controls and extends antacid activity	Egraine*‡ . . . . .	45 mg.

AVAILABLE IN BOXES OF 100 TABLETS, SPECIALLY STRIPPED FOR EASY CARRYING  
 \*Cyanopsis tetragonoloba gum      †Protein binder from oat      ‡Trade Marks



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constipating effects,  
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This clinician concludes: "Magnesium aluminum hydroxide gel is more palatable than aluminum hydroxide gel and better suited to the prolonged administration required for the antacid therapy of peptic ulcer and hyperchlorhydria."<sup>1</sup>

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*Samples sent promptly on request.*



<sup>1</sup> Morrison, Samuel: Magnesium aluminum hydroxide gel in the antacid therapy of peptic ulcer. Am. J. of Gastroenterology 22:309 (Oct.) 1954.



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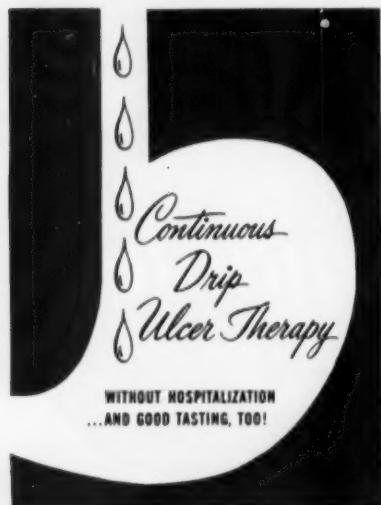
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\*Steigmann, F., and Goldberg, E.: Ambulatory Continuous Drip Method in the Treatment of Peptic Ulcer, Am. J. Digest. Dis. 22:67 (Mar.) 1955.

†Mg trisilicate 3.5 gr.; Ca carbonate 2.0 gr.; Mg oxide 2.0 gr.; Mg carbonate 0.5 gr.

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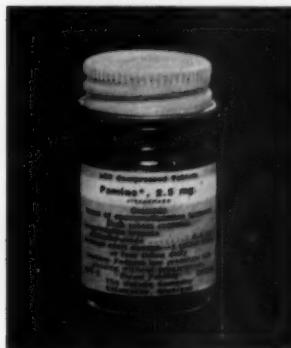
Methscopolamine bromide

2.5 mg.

*Average dosage (ulcer):*One tablet one-half hour before  
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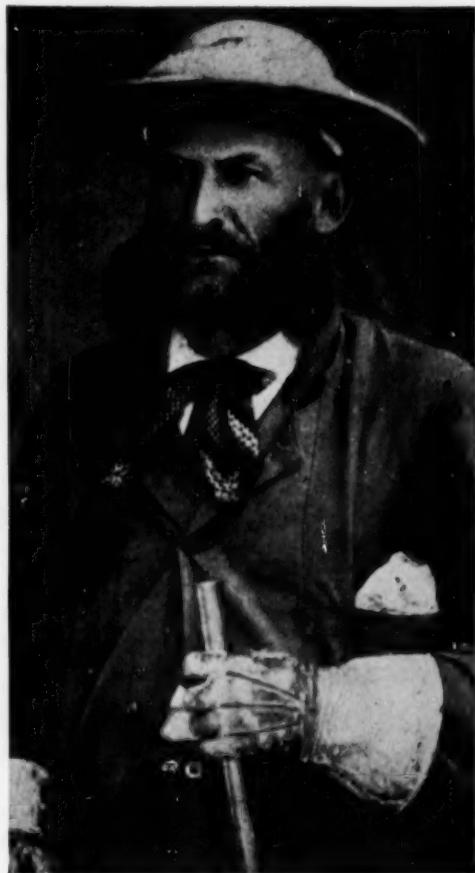
It was not Crook's first Indian, nor his last. By the time he made general, Crook was the greatest Indian-fighter this country has ever had.

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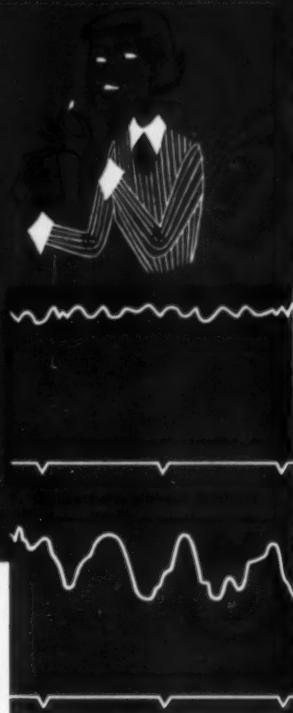


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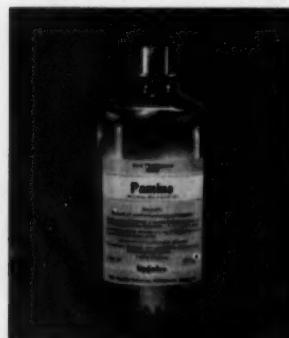
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1. Hoffmann, C. R.: Am. Pract. & Digest Treat. 4:464, 1953.

2. Riese, J. A.: Am. J. Digest. Dis. 21:81, 1954.

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